FACULTEIT LANDBOUWKUNDIGE
EN TOEGEPASTE BIOLOGISCHE
WETENSCHAPPEN

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NEW ENTRIES TO 2,4-METHANOPROLINE DERIVATIVES

NIEUWE TOETREDINGSWEGEN TOT 2,4-METHANOPROLINE DERIVATEN

door

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VOORWOORD

Anyone who has never made a mistake has never tried anything new (Albert Einstein).

Toen ik vier jaar geleden begon aan mijn doctoraal proefschrift had ik me nooit kunnen inbeelden dat de tijd zo rap voorbij zou vliegen. Mijn eigenlijke doctoraat begon bij het schrijven van mijn IWT-project. In dit project werden vele reacties uitgeschreven en geargumenteerd, maar de theorie wil al wel eens verschillen van de praktijk. Deze doctoraatsperiode bestond dan ook uit een opeenvolging van ups en downs. Er waren periodes waar de meest voor de hand liggende reacties mijn beginproduct omtoverden tot een bruine (soms zwarte) ondefinieerbare massa. En zoals mijn promotor steeds zei: 'Kleur wil niets zeggen, maar zwart is meestal niet goed', en gelijk had hij. Maar hoe dieper het dal, des te groter was de triomf wanneer ik erin slaagde om een dergelijke reactie toch tot een goed einde te brengen. Het lukken of mislukken van een reactie is inherent aan scheikunde.

Aan een doctoraat begin je uiteraard niet alleen, je moet een promotor hebben. Een promotor heeft ook een aantal taken. In eerste instantie moet hij de doctorandus in de beginfase helpen bij het genereren van een onderwerp en duiden op eventuele moeilijkheden en gevaren bij bepaalde reacties. Anderzijds moet hij na deze beginperiode de doctorandus de vrijheid geven om eigen ideeën te genereren en die aan de praktijk te toetsen. Mijn promotor, Prof. dr. ir. C. Stevens, is een 'jonge prof' volgens academische normen. Bij het begin van mijn doctoraat en ook tijdens mijn ingenieursthesis werkte Prof. Stevens schuin tegenover mij aan de labotafel. Dit heeft veel voordelen naar begeleiding toe, maar het nadeel is dat beginnersfouten niet ongemerkt voorbijgingen. Ik ben Prof. Stevens veel dank verschuldigd, niet alleen voor de begeleiding de voorbije jaren, maar ook voor de vrijheid die ik heb genoten als doctoraatsstudent. Eens mijn eigen ideeën de kop op staken, stond hij steeds open voor discussie en gaf opbouwende kritiek. Wanneer ik een idee had waar hij de kans op slagen klein achtte, kreeg ik wellicht de belangrijkste zin in wetenschappelijk onderzoek: 'Ik denk niet dat het gaat lukken, maar je mag het proberen'. Aangezien ik Thomas 'de ongelovige' ben, probeerde ik het steeds. In de meeste gevallen moest ik me echter neerleggen bij de wetten der chemie, maar het zijn die uitzonderlijke gevallen waar het toch lukte die scheikunde zo boeiend maken. Een dergelijke reactie werd dan steevast bestempeld als: 'een pintreactie', vroeger ook wel eens 'een cognacreactie' genoemd. Een noodzakelijk kwaad bij wetenschappelijk onderzoek is het schrijven van artikels. Ik moet ook hiervoor Prof. Stevens bedanken voor de stimulans en het geduld wanneer ik in de pen kroop.

Tevens wens ik de leden van de lees- en examencommissie te danken voor het kritisch doornemen van dit werk.
Een speciaal woordje van dank voor Dr. Laurent De Buyck. Hij is degene waar ik steeds terecht bij kon voor reactieomstandigheden en het passief roken van een halve sigaar (afhankelijk van het aantal uitwijdingen en levensbeschouwingen was dit een ganse sigaar).

De sfeer in het labo wordt uiteraard bepaald door de vele thesis- en doctoraatsstudenten. Daarbij denk ik zeker aan de huidige: Inge, Tina, Ellen, Vera, Kristof, Bart, Nicolai, Rafal (de 'Stevens group'), David, Guido, Matthias, Bram, Willem, Sven, An, Erick, Nicola, Tuyen, maar tevens aan degenen van de afgelopen 4 jaar in het labo vertoefden. Ik had tevens het genoegen om mijn bureau te delen met Kourosch, Guido, Inge en Tuyen. Ik ben er spijtig genoeg niet in geslaagd om Tuyen mijn naam te leren en ga dus verder door het leven als Tomàc. De vlotte samenwerking met 'mijn' thesisstudenten Wannes, David, Bram, Nicolai en Wouter werd zeer gewaardeerd.

I thank David Mitchell for reading and correcting my thesis. I am aware that this must have been a real slog for someone unfamiliar with the chemical jargon. Thanks again, not only for reading but also for the nice holidays I had during my childhood in East Sussex.

De meeste dank ben ik echter verschuldigd aan mijn ouders. Ik laat het misschien te weinig merken en daarom lijkt dit mij een uitgelezen gelegenheid om jullie nog eens in de bloemetjes te zetten. Jullie hebben me beiden steeds gesteund, niet alleen bij mijn studies, maar tevens bij de verbouwingen en de inrichting van ons huis. Eender wat, of gelijk wanneer ik iets nodig had, was Brussel maar één telefoontje van Gent verwijderd. Bedankt voor de steun van de voorbije jaren en dat er nog veel mogen komen.
Ik wil tevens al wie op de een of andere manier heeft bijgedragen tot de realisatie van dit werk danken: mijn schoonouders en schoonfamilie, mijn familie, Bram (mijn broer), oma's, ooms en tantes, vrienden (Stevens & Laura, Nathalie & Bart, Sara & Henri, Fanny, Alain) en 'Flamingo'-buren. Jullie waren zeer verdraagzaam, vooral dan tijdens de eindfase van mijn doctoraat waar ik jullie wellicht verwaarloosd heb.
Rest mij in het bijzonder nog Els (mijn echtgenote) een dikke bees te geven voor de steun en hulp de afgelopen jaren. Het was niet gemakkelijk om met twee op het zelfde moment een doctoraat te schrijven maar we hebben ons daar zonder slag of stoot kunnen doorworstelen. Wat de toekomst zal brengen weet niemand, maar ik ben ervan overtuigd, en ik ga het met de woorden van iemand anders zeggen: 'What you say, becomes'. BEDANKT!

Thomas Rammeloo
Gent, september 2003

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List of abbreviations

ACE-Cl = 1-chloroethyl chloroformate

AIBN = 2,2'-azobisisobutyronitrile

BHT = 2,6-di-t-butyl-4-methylphenol

Boc-BMI = 1-(t-butoxycarbonyl)-2-t-butyl-3-methyl-4-imidazolidinone

CAN = cerium ammonium (IV)nitrate

CSI = chlorosulfonyl isocyanide

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DEAD = diethyl azodicarboxylate

DiBAl = diisobutylaluminium hydride

DMSO = dimethyl sulfoxide

EAATs = excitatory amino acid transporters

EWG = electron withdrawing group

HMDS = hexamethyldisilazane

KHMDS = potassium hexamethyldisilazane

KOtBu = potassium t-butoxide

LDA = lithium diisopropylamide

LiHMDS = lithium hexamethyldisilazane

L-selectride = *L*-tri-sec-butylborohydride

NBA = *N*-bromoacetamide

NBS = *N*-bromosuccinimide

P = protecting group

PPIase = peptidyl-prolyl *cis/trans* isomerase

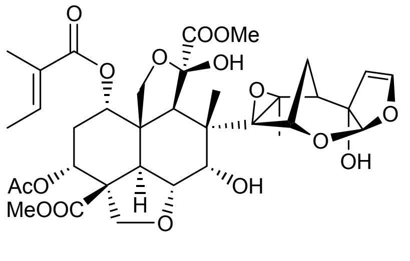
PPTS = pyridinium p-tolunenesulfonate

RT = room temperature

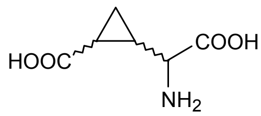
THF = tetrahydrofuran

1. Introduction

It is estimated that yearly almost 15% of the world's food production is lost due to attack of the stored reserves by insects and seed predators.[1,2] To meet the demand for food of the expanding world population, there is certainly a need of new ways to protect plant crops against predators and pathogens. In this context the use of chemicals can not be avoided, however, the western world aims not only at a maximal production, but also the improvement of the quality of the crop has become of great importance. The integrated agriculture constantly looks for new insecticides which are based upon natural products such as azadirachtine **1**, isolated from *Azadirachta indica*.[3] These new products have a selective insecticidal activity, based upon repellent and anti-feedant properties.[4,5,6,7] The extraction from the natural resource is not always feasible on large scale.[8] Therefore, such a compound is usually seen as a lead structure to prepare analogues with the same or enhanced activity.[9] One of the frequently used defence mechanisms of plants against predators is the accumulation of high quantities of non-protein amino acids in the seeds. The 2-(carboxycyclopropyl)glycine **2** is a glutamic acid analogue for which strong evidence exists that it influences the food consumption of insects. This amino acid was isolated from an *Ephedra* species.[10] 2,4-Methanoproline **3** is another amino acid isolated from the seeds of *Ateleia Herbert-smithii Pittier*.[11,12] Not only the seeds contain this amino acid but it has also been isolated from the leaves. Later, 2,4-methanoproline has been isolated from four other *Ateleia* species and from the closely related *Cyanthostegia* species,[13,14] and from different species of the genus *Bocoa*[15] (Leguminosae; Papilionoideae). The seeds of *Ateleia Herbert-smithii Pittier* are avoided by more than 100 different seed predators, among which numerous insects and rodents. There is only one monophagous insect species, a moth, and a few insects from which the larva are extremely gluttonous, which eat these seeds. The leaves of the tree are also neglected by vertebrate herbivores. It is since the isolation and characterisation of 2,4-methanoproline that some authors attribute anti-feedant properties to this amino acid. Not only 2,4-methanoproline **3** but also 2,4-methanoglutamic acid **4** and *cis*-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid[14] **5** were isolated from this tree. A fourth compound, 2,4-methanopyroglutamic acid **6**, although not isolated, was proposed as a possible seed component or an intermediate in the biosynthesis of the other three amino acids.[16]



Azadirachtin 1



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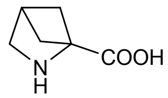
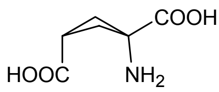


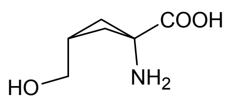
3

2,4-methanoproline



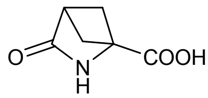
4

2,4-methano-glutamic acid



5

***cis*-1-amino-3-hydroxy-methyl-cyclobutane-1-carboxylic acid**



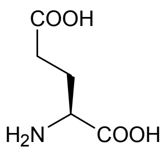
6

2,4-methano-pyroglutamic acid

The main problem is that no real screening of the biological activity of 2,4-methanoproline has been performed. It is because of the rare 2-azabicyclo[2.1.1]hexane skeleton that the anti-feedant activity was attributed to this compound. To our knowledge, only one screening was done in 1984.[17] In the experiment the extract of the seeds, containing 2,4-methanoglutaminc acid and 2,4-methanoproline, was mixed into laboratory chow at an equal concentration to that present in these seeds. *L. Salvini,* a small rodent which normally rejects the seeds, ate the adulterated chow with gusto and grew fat on it. Since this screening was performed only on a rodent, the rejection of the seeds by insects and other predators remains very much a mystery.

2. Goal

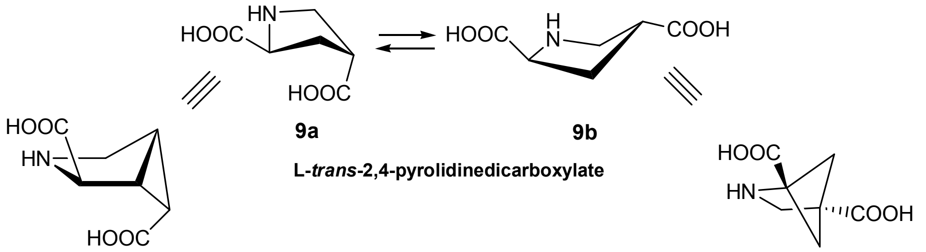
Pyrrolidines are common to many biological significant molecules.[18] In the search for selective biological molecules, one useful strategy is to incorporate this key pharmacophoric entity into a less flexible model such as the 2-azabicyclo[2.1.1]hexane skeleton or other conformationally restricted skeletons.[19] Because of the bicyclic structure, the 2-azabicyclo[2.1.1]hexane skeleton further diminishes the flexibility of the system and as a consequence a conformationally rigid structure is obtained. The pharmacophore groups connected to such a skeleton have therefore a defined orientation in space and provide useful information on receptors by evaluating the structure activity relationship.



7

***L*-Glutamic acid**

An example of this, is 2,4-dicarboxyl-2,4-methanopyrrolidine **10**, a derivative of 2,4-methanoproline, which is more active than the 2,4-pyrolidinedicarboxylate **9a,b**.[20] The 2,6-dicarboxyl-3-azabicyclo[3.1.0]hexane **8** is also a conformationally restricted analogue of glutamic acid **7** but because of the conformational properties this molecule acts as an antagonist of glutamic acid, whereas 2,4-pyrolidinedicarboxylate **9a,b** is an agonist of glutamic acid **7**. *L*-Glutamic acid is a very important neurotransmitter in the central nervous system of mammals. This illustrates nicely how bicyclic conformational restricted analogues can give valuable information about the conformation of the active compound which it mimics.



9a **9b**

L-*trans*-2,4-pyrolidinedicarboxylate

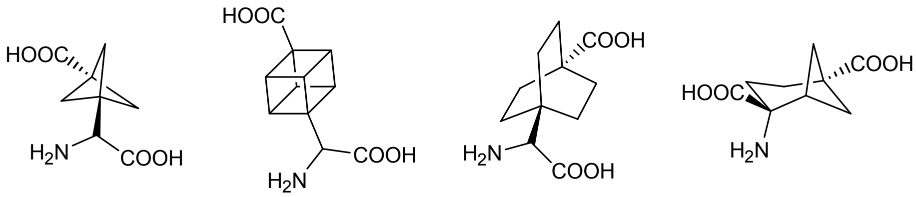
8

2,6-dicarboxyl-3-azabicyclo[3.1.0]hexane

10

2,4-dicarboxyl-2,4-methanopyrrolidine

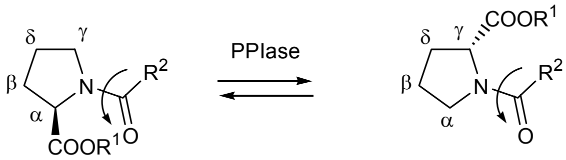
Because of the importance of glutamic acid in the central nervous system, much research has been performed on cyclic and bicyclic analogues such as **11**, **12**, **13** and **14**.[21] Certain membrane proteins (EAATs: excitatory amino acid transporters) play an important role in the regulation of the glutamic acid concentration, preventing a too high extracellular concentration of glutamic acid which leads to excitoxicity. Selective inhibitors such as **8** and agonists with a high activity such as **10** give much valuable information about the interaction of EAATs with certain pharmacophore groups. They are very useful in the research concerning the mechanism and the function of these transporter proteins.



11 **12** **13** **14**

This research is of great importance for the development of pharmacological probes and drug candidates for the treatment of neurological disorders including pain, epilepsy and various chronic neurodegenerative diseases such as Huntington disease and Altzheimer.

Further, 2,4-methanoproline **3** does not behave like classical amino acids. It has first of all a bicyclic structure and is achiral unlike the ‘normal’ amino acids. As a proline analogue it possesses some very interesting features. First, the importance of proline in proteins is highlighted. Proline and hydroxyproline are unique amino acids since they form a tertiary instead of a secondary peptide bond when they are introduced into proteins. Most amino acids stabilise selectively the *trans* peptide bond. This *trans* form is at least 10 kcal/mol more stable than the *cis* form, and for this reason amino acids usually possess a *trans* peptide bond. In peptides which contain proline, there is only a slight energy difference between the *trans* and the *cis* peptide bond. The *trans* form is only 2 kcal/mol more stable than the *cis* form, and thus allowing the *cis/trans* isomerisation in peptides.[22,23,24] This is illustrated in Figure 1.



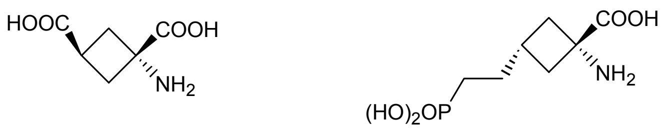
15 *Trans*   **16** *Cis*

Figure 1: *Cis-trans* isomerisation of peptides containing proline

This isomerisation is of crucial importance and determines biological and pharmacological properties of proteins and peptides. *In vivo* this isomerisation is catalysed by peptidyl-prolyl *cis/trans* isomerases (PPIase).[24] These enzymes play an important role in the cell metabolism. By isomerisation of such a peptide bond, a protein (transporter protein, receptor molecule, enzyme, …) can be activated or deactivated. The isomerisation is probably also the rate determing step in the folding of peptides and enzymes.[24] The research concerning this isomerisation is strongly influenced by replacement of proline in a certain peptide by a proline analogue, which selectively stabilises either the *trans* or the *cis* peptide bond.[22,23,25,26,27] In that case no isomerisation can take place. By evaluating the activity of the modified enzyme, conclusions can be drawn concerning the peptide bond adjacent to proline.

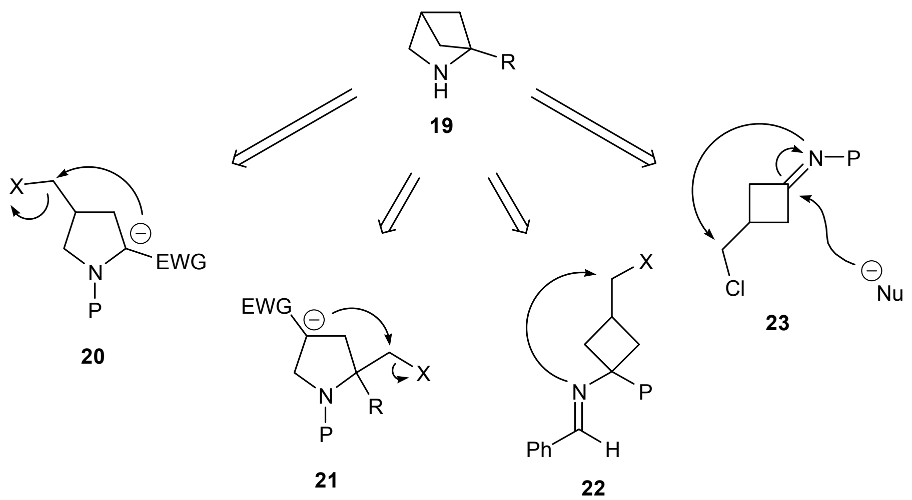
Energy studies on proteins which contain 2,4-methanoproline **3** indicate that this amino acid selectively stabilises the *trans* peptide bond with more than 5.9 kcal/mol.[28,29,30,31,32] Although this is less than for other amino acids, usually > 10 kcal/mol, it is sufficient to obtain for 95% the *trans* peptide bond. Therefore, the synthesis of proline analogues is very interesting and one of the reasons why this research was conducted towards 2,4-methanoproline.

Not only 2,4-methanoproline but also the structure of 1-aminocyclobutane carboxylic acids has received an increasing attention in the field of medicinal chemistry in recent years. In 1990, *trans*-2,4-methanoglutaminic acid **17** was described as a highly potent NMDA agonist,[33] whereas other 1,3-disubstituted cyclobutane derived α-amino acids such as **18** operate as NMDA antagonists and anticonvulsive drugs.[34] Furthermore, incorporation of various 2,4-methano amino acids into bioactive peptides increased their biological stability towards enzymatic degradation and altered their biological properties remarkably.[35]

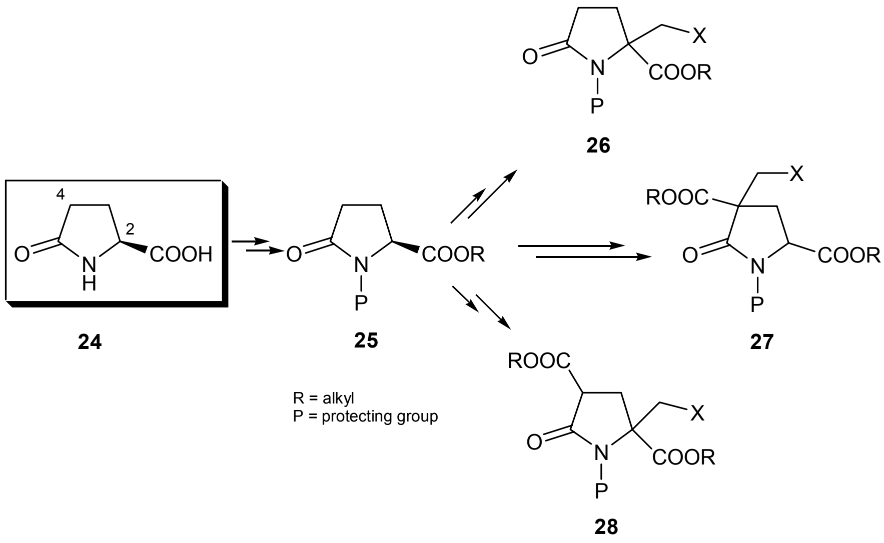


17   **18**

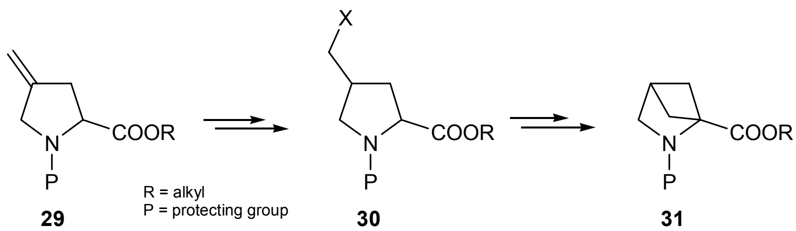
The first synthesis of 2,4-methanoproline **3** dates from early 1980. It consisted of a light induced [2+2]-cycloaddition to prepare the 2-azabicyclo[2.1.1]hexane skeleton. Such a synthesis is valuable but has the disadvantage of being less convenient for the synthesis of analogues of 2,4-methanoproline. Therefore, the aim of this PhD thesis was to develop new entries to 2,4-methanoproline and analogues. Retro-synthetically, four major pathways will be evaluated.



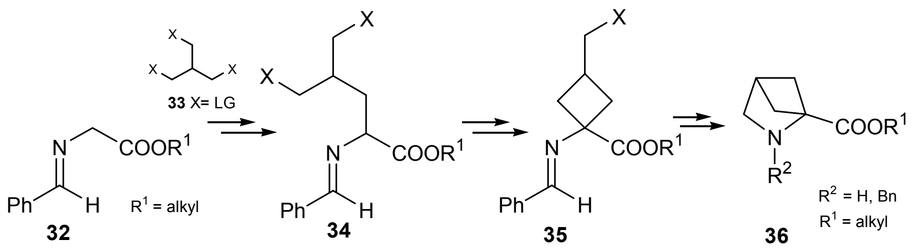
In the first two routes, attempts will be undertaken to construct the 2-azabicyclo[2.1.1]hexane skeleton by formation of a 4-membered ring in an existing 5-membered pyrrolidine ring. This will probably be the most difficult pathway since the strained 4-membered ring is constructed last. To prepare such precursors, **20** and **21**, a great deal of attention will be paid to *L*-pyroglutamic acid **24** as chiral starting material. Although it is not necessary to use an enantio pure starting material (since the end product is achiral) it might give interesting chiral intermediates. Besides, pyroglutamic acid is rather cheap and opens a lot of possibilities to prepare derivatives. Another advantage is that the 2 and the 4 position of the pyroglutamate ring are already activated and different selective alkylations have been described in literature (see literature overview). By a good choice of the protecting groups, alkylation will be performed on **25** and after reduction of the amide, the desired pyrrolidine ring would be obtained. As mentioned before, glutamic acid is one of the major neurotransmitters in the central nervous system of mammals. Therefore, much research was performed to prepare analogues of glutamic acid and to evaluate the affinity of these compounds for certain receptors.[36]



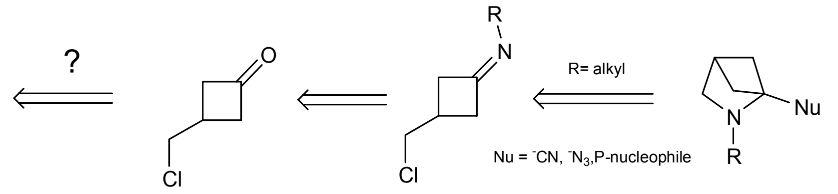
Not only pyroglutamic acid **24** will be used to prepare pyrrolidines, but also the amino ester **29** will be evaluated as starting material in the synthesis of 2-azabicyclo[2.1.1]hexanes. This pathway will probably be shorter because less functional group transformations have to be carried out. On the other hand it will be less convenient to prepare analogues.



In a third pathway, reactions will be evaluated to construct the 2-azabicyclo[2.1.1]hexane skeleton by alkylation of imines of the type **32** with a suitable electrophile. After hydrolysis or reduction of the imine **35**, the desired bicyclic skeleton could be obtained.



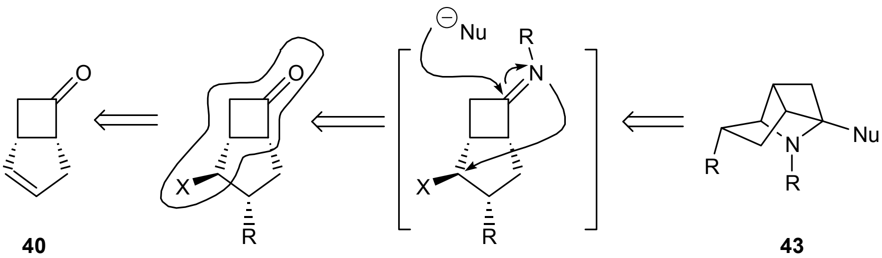
Attempts will also be undertaken to construct the 2-azabicyclo[2.1.1]hexane skeleton and 2,4-methanoproline starting from a suitable γ-halomethylcyclobutanone **37**. Such a pathway has already proven to be successful, but the main problem in this approach is the absence of a good synthetic procedure to prepare such a cyclobutanone.[37] Therefore, a great deal of effort was performed to develop new entries to this type of compounds.



37 **38** **39**

Once a good procedure is available, 3-(chloromethyl)cyclobutanone **37** will be converted to the corresponding imine **38** and different nucleophiles will be evaluated to prepare analogues with the 2-azabicyclo[2.1.1]hexane skeleton.

This pathway could be extended to include even more constrained tricyclic structures. The idea is to use a suitable bicyclic starting material **40** and evaluate the ring closure of the corresponding imines **42**. This methodology would lead to tricyclic proline analogues with a very rigid and defined structure.



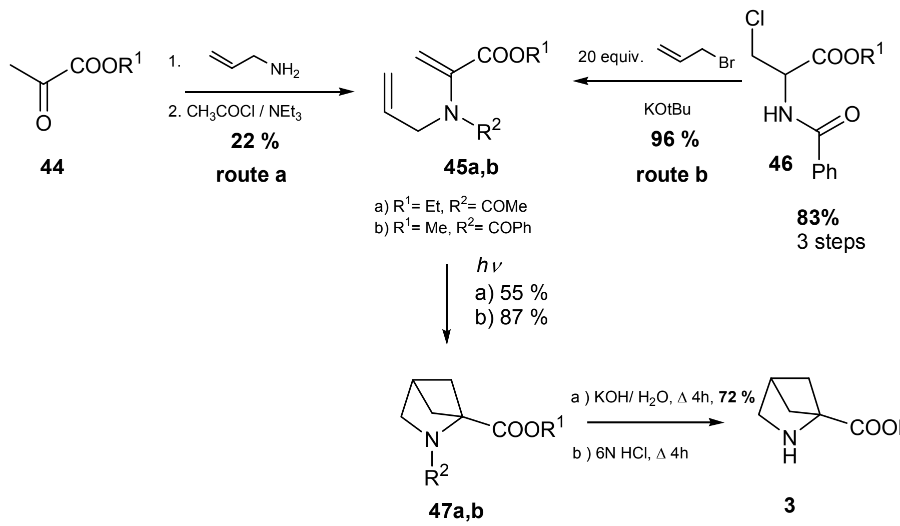
40 **41** **42** **43**

In a last topic, all synthesised 2-azabicyclo[2.1.1]hexanes will be tested for their anti-feedant properties. This is very important since no real screening has been performed on the natural 2,4-methanoproline (and certainly not on its derivatives) in order to attribute the suggested activity to this compound. The detection of improved anti-feedant activity for one of the compounds could open an interesting agricultural application to prevent grains from predator attack.

3. Literature overview

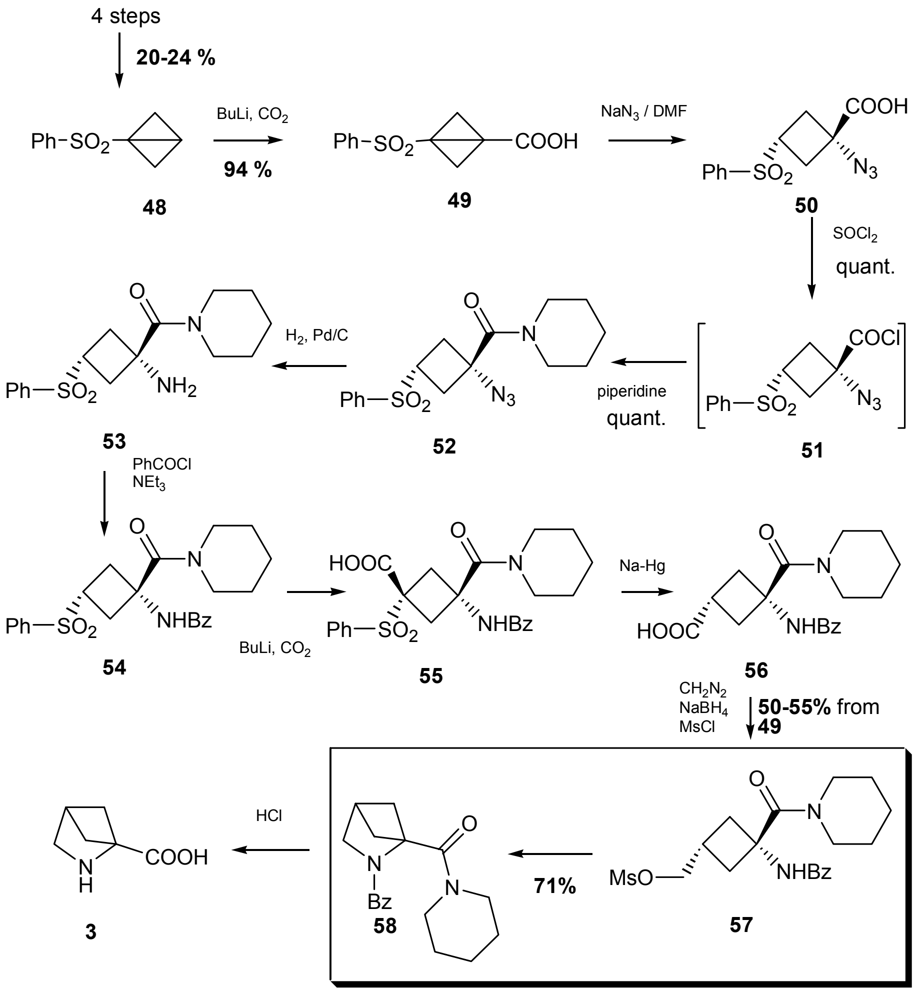
3.1. Synthesis of the natural 2,4-methanoproline

The 2-azabicyclo[2.1.1]hexane skeleton is very rare in nature and 2,4-methanoproline is up to now the only known natural amino acid containing this skeleton.[11,12,15] From the chemical point of view this is a very constrained bicyclic compound and therefore a real challenge to synthesise. Most of the available procedures to prepare the 2-azabicyclo[2.1.1]hexane skeleton use a light-induced intramolecular [2+2]-cycloaddition as a key step. Using such a mechanism the 4- as well as the 5-membered ring are constructed simultaneously. In a way, the utilisation of a cycloaddition reaction is not surprising since many compounds containing a 4-membered ring are constructed by such a mechanism. The first synthesis of 2,4-methanoproline was conducted immediately after its isolation in nature in the early 1980's. In the key step, an appropriate diene **45a**,**b** was cyclised via a [2+2]-cycloaddition to the precursor of 2,4-methanoproline. This diene could be prepared in two different ways using ethyl pyruvate **44** or serine as a starting material (route a[38] or b[16,39]).



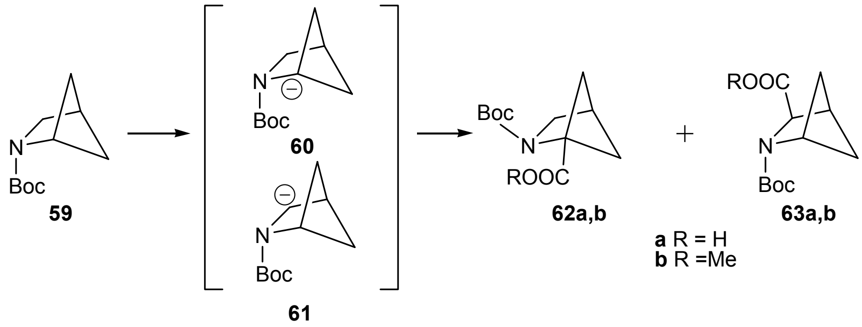
Once the precursors **47a,b** were prepared, they were hydrolysed in acidic or basic medium and 2,4-methanoproline **3** was obtained. The main problem of this pathway is that the cycloaddition step could only be performed on a rather small scale and the reaction had to be conducted in a very diluted form. This makes upscaling rather difficult because the reaction was done while irradiating with UV-light (300 nm).

Another pathway leading to 2,4-methanoproline used an intramolecular nucleophilic substitution as a key step. This method was developed by Gaoni who used 1-(arylsulfonyl)-bicyclo[1.1.0]butane **48** as starting material.[40,41,42,43] This compound **48** was prepared in 4 steps from phenyl methyl sulfone (the yield is however low 20-24%). The next synthetic steps all have high yields. The overall yield to prepare **56** was 50-55 % starting from **49**. Although the pathway is long, the ring closure of the cyclobutane derivative **57** using BuLi as base has a high yield (71**%**).[44,45,46] An important conclusion is that the bicyclic skeleton can be prepared by first constructing the 4-membered ring followed by ring closing to obtain the 2-azabicyclo-[2.1.1]hexane skeleton.



The main problem is the absence of a suitable pathway to the cyclobutane precursors such as **57**. Because many functional group transformations were necessary to make the right precursor, the pathway is lengthy and thus an inconvenient way to prepare 2,4-methanoproline on large scale.

Only one alternative pathway, described by Krow, led to a precursor of the natural 2,4-methanoproline **3**.[47] In this reaction sequence, a *N*-Boc-2-azabicyclo[2.1.1]hexane **59** was deprotonated using the very strong base sec-butyllithium at 0°C to afford the C_1 bridgehead α-lithio anion **60**. Quenching the anion with carbon dioxide or methyl chloroformate provided the bridgehead acid **62a** or ester **62b** in very good yields (Table 1).

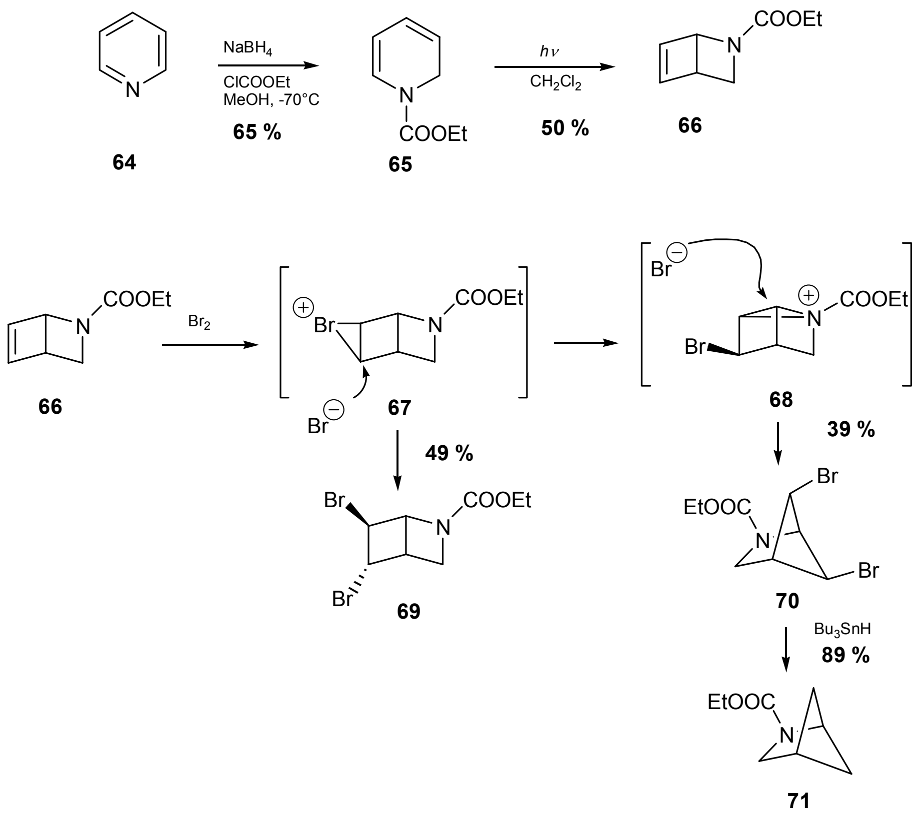


The reaction temperature is a very important parameter: at 0°C, only the 2,4-methanoproline analogues **62a** and **62b** were obtained (see Table 1), but at -78°C a mixture of regioisomeric methylene and bridgehead anions were formed which led to mixtures of regiomeric methylene and bridgehead acids or methyl esters after quenching.

Table 1: Lithiation of azabicycle **59** and electrophilic additions to provide methylene **63a,b** and/or bridgehead **62a,b** products

Electrophile	*s*-BuLi	T	R =	Product	Ratio **62**/**63**	Yield
CO_2	1.2 equiv.	0°C	H	62a		98 %
ClCOOMe	1.2 equiv.	0°C	Me	62b		70 %
CO_2	1.2 equiv.	-78°C	H	62a/63a	57/43	76 %
ClCOOMe	1.2 equiv.	-78°C	Me	62b/63b	50/50	81 %

The main drawback of this approach is the preparation of the *N*-Boc-2-azabicyclo[2.1.1]hexane **59**. This compound was prepared from pyridine in a 4-step sequence. The actual yield could not be retrieved in the literature since the authors refer to one of their previous articles, [48,49,50] in which the N-COOEt[51] compound **66** and not the N-Boc derivative is reported.

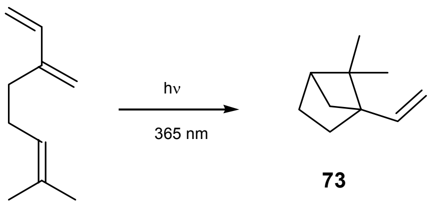


The key synthetic intermediate, *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene **66** was brominated and a mixture of unrearranged dibromide **69** (yield = 49 %) and the rearranged dibromide **68** (yield = 39 %) was obtained which were separated. The two bromide atoms of **70** were removed through a free radical reduction process using Bu_3SnH (yield = 89 %). At least 6 synthetic steps are necessary to prepare 2,4-methanoproline if the deprotection of the N-alkyloxycarbonyl group is taken into account. Some steps have a relatively low yield.

3.2. Synthesis of analogues of 2,4-methanoproline

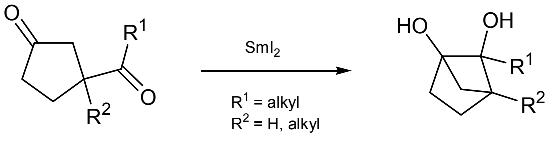
3.2.1. Entry to bicyclo[2.1.1]hexanes

To obtain a good insight in the mechanisms for the construction of the 2-azabicyclo[2.1.1]hexane skeleton, pathways leading to the C-analogue (bicyclo[2.1.1]hexane) are summarized. Light induced [2+2]-cycloaddition reactions are widely used to construct this bicyclic skeleton[52] or more complex structures[53] containing this bicyclic system.



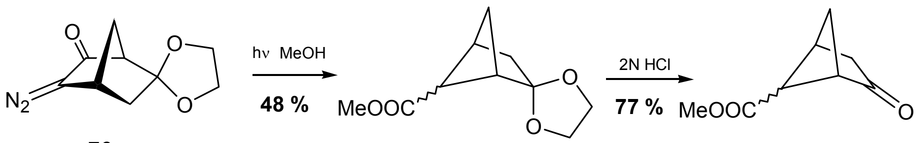
72 73

Samarium iodide is a very good reagent to prepare polycyclic 1,2-diols such as **75** by a SmI_2-mediate pinacol[54] coupling.[55,56]



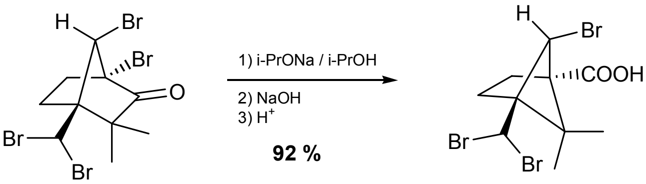
74 15-81 % 75

On the other hand, rearrangements sometimes lead to substituted bicyclo[2.1.1]hexanes which are difficult to prepare using other mechanisms. For instance the Wolff rearrangement[57,58] converts a 3-diazobicyclo[2.1.1]heptan-2-one such as **76** to compound **77** which led to the very constrained bicyclic structure **78**, after hydrolysis of the acetal.[59]



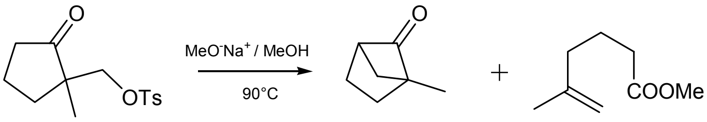
76 77 78

Another interesting and high yielding pathway uses the bromo substituted camphor derivative **79** which could be converted through an intramolecular cyclisation-Favorskii rearrangement reaction sequence to **80**.[60] Other rearrangements using camphor as starting material have been described in literature leading to the bicyclo[2.1.1]hexane skeleton in high yield.[61,62]



79 80

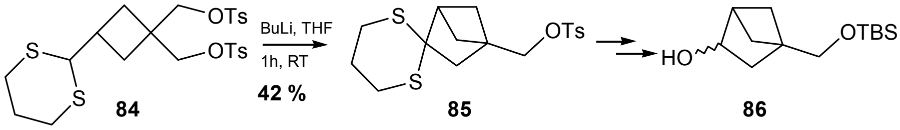
Rarely the bicyclo[2.1.1]hexane skeleton is prepared through an intramolecular ring closing sequence. In the case of **81**, the 4-membered ring could be synthesised in the existing 5-membered ring, but with a low yield (18 %).[63]



81 **82** **83**

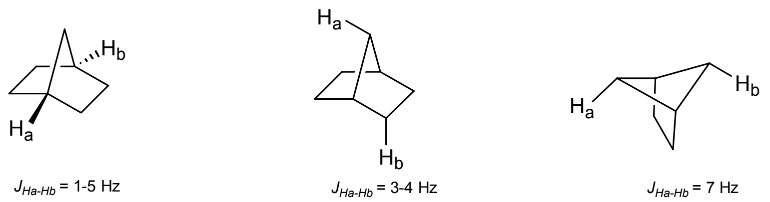
18 % 63 %

The bicyclic structure has also been prepared by intramolecular ring closing of a suitable cyclobutane derivative such as **84.**[64] Treatment of compound **84** with BuLi led to the desired bicyclo[2.1.1]hexane skeleton. Product **86** has been used for the preparation of conformationally locked nucleosides.

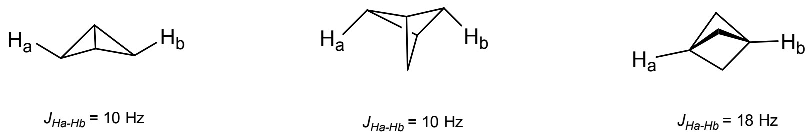


84 **85** **86**

Interestingly, due to the constrained structure some long range proton spin-spin coupling constants can be observed (between H_a and H_b) in bicyclic compounds. This can be explained by the W-conformation and the distance between the carbons involved.[65] Some examples are depicted in the scheme below.



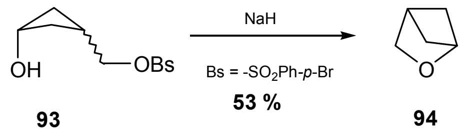
87 **88** **89**



90 **91** **92**

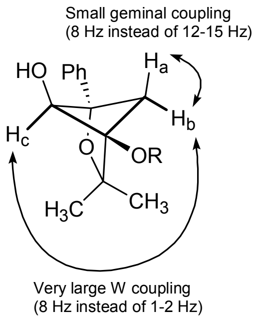
3.2.2. Entry to the 2-oxabicyclo[2.1.1]hexane skeleton

The 2-oxabicyclo[2.1.1]hexane skeleton can be synthesised through different procedures. A frequently used reaction mechanism is once more the light induced [2+2]-cycloaddition.[66] For our research the entry of Kirmse is however more interesting.[67]



93 **94**

The ring closure was performed by deprotonating the alcohol **93** and ring closure to a –CH_2OBs group in the 3-position. Two other examples using an intramolecular nucleophilic substitution have been described to prepare the 2-oxabicyclo[2.1.1]hexane skeleton.[68,69,70]



95

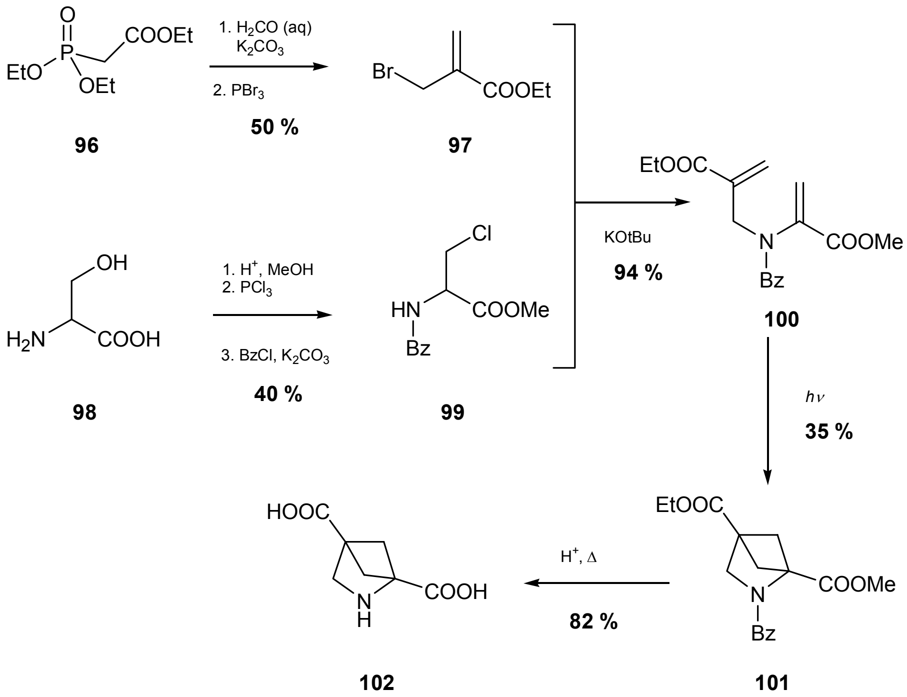
Some very remarkable coupling constants can be found in such a skeleton. In compound **95**[69] there exists a very large W-coupling between the two endo-oriented protons H_b and H_c (*J*= ~8Hz instead of 1-2 Hz). This large coupling can be attributed to the very constrained structure of **95** and the perfect W-conformation between H_b and H_c. On the other hand the geminal coupling between H_a and H_b is rather small, only 8 Hz, instead of the expected 12-15Hz.

3.2.3. Entry to the 2-azabicyclo[2.1.1]hexane skeleton

3.2.3.1. Via a light induced [2+2]-cycloaddition

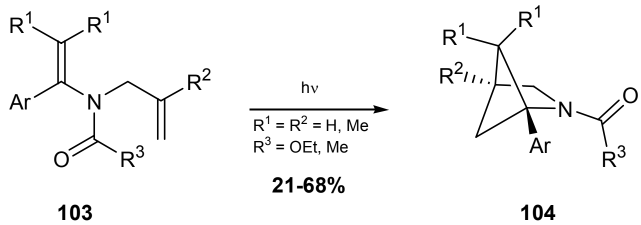
As mentioned earlier, a [2+2]-light induced cycloaddition is a convenient reaction to prepare the bicyclic skeleton in one step from a suitable diene.[71] This pathway has however some drawbacks and limitations. First of all one of the two alkenes should be electron rich and the other electron poor to isolate the end product in high yields. Secondly, the reaction has to be performed in diluted solutions (usually < 4%) under irradiation conditions which make upscaling difficult.

As mentioned earlier 2,4-methanoproline **3** has the ability to stabilise selectively the *trans*-peptide bond when it is introduced into a peptide. Because of the basic skeleton, this molecule has a very rigid 3D-structure. Therefore, 2,4-dicarboxy-2,4-methanopyrrolidine **102** was prepared to mimic glutamic acid and to investigate the sodium dependent glutamic acid dependent transporter protein.[20]

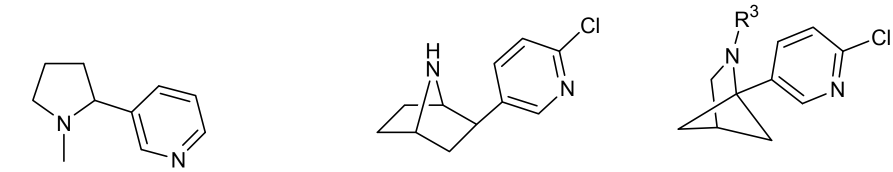


This synthesis proceeds via a light induced intramolecular [2+2]-cycloaddition. The diene was prepared from serine **98** and triethyl phosphonoacetate **96**. This pathway is a clear presentation of one of the drawbacks of the [2+2]-cycloaddition reaction. In most cases an electron rich alkene is reacted with an electron deficient one. In this specific case, neither of the alkenes is electron rich which explains the relatively low yield of the reaction.

Another example where the constrained 2-azabicyclo[2.1.1]hexane skeleton is used to mimic a biological active compound was described by Piotrowski.[72]



A number of 1-aryl and 1-pyridyl-2-azabicyclo[2.1.1]hexanes **104** were prepared by an intramolecular [2+2] photo-cycloaddition reaction mimicking either nicotine[73] **105** or epibatidine[74] **106**, an alkaloid isolated from the skin of the frog *Epipedobates-tricolor* in 1976 by John Daly.

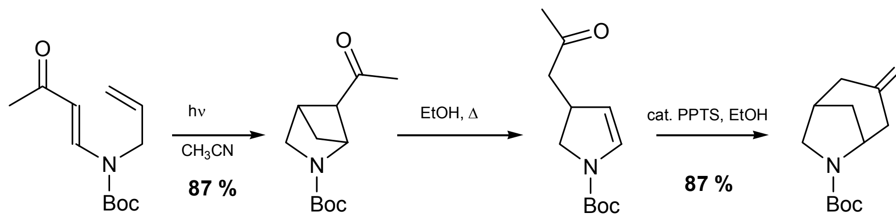


105 **106** **107** R^3 = Me, H

nicotine **epibatidine**

Both compounds display potent biological activity in mammals by modulation of the nicotinic acetylcholine receptor.[75] As both **105** and **106** are highly toxic and lack receptor selectivity, analogues such as **107** are very interesting because they might provide more information about ligand-receptor interactions.

The 2-azabicyclo[2.1.1]hexane skeleton is not only the basic structure of 2,4-methanoproline **3**, it has also been prepared as an intermediate in more complex compounds.
The 1-(*N*-allylamino)-1-butene-3-on **108** was converted to **109** in good yields (an electron rich and an electron poor alkene are present) and was subsequently converted in 2 steps to **111**.[76]

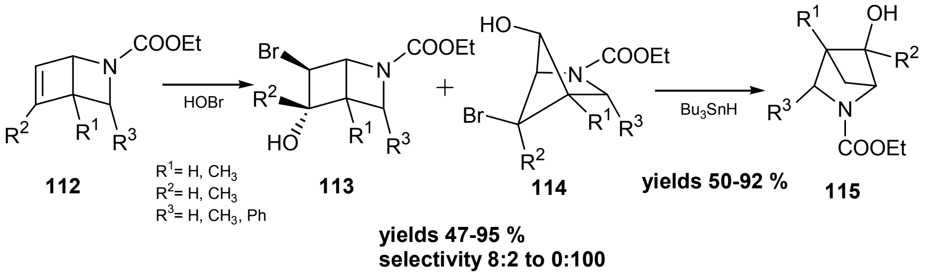


108 **109** **110** **111**

The azabicyclo[3.2.1]octanones are widespread in nature and are important ring systems for the development of analgesics[77] and muscarinic[78] antagonists.
The 2-azabicyclo[2.1.1]hexane skeleton has also been used as an intermediate in the ABC substructure of taxane.[79]

3.2.3.2. By rearrangement of *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene

A novel approach to construct the 2-azabicyclo[2.1.1]hexane skeleton was developed by Krow. The starting material is N-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene **112** which was prepared from pyridine. The electrophilic addition of HOBr to the double bond gave rise to compounds **113** and **114** (ratio 8:2-0:100). The intermediate bromonium species formed during this reaction can be attacked either at the C5-carbon atom by $^-$OH or at the C6-carbon atom by nitrogen. In the first case, this leads to compound **113,** in the latter case to an aziridinium species (see also reaction scheme on pages 11-12) which is attacked by $^{-}$OH to form **114**.[48,80]



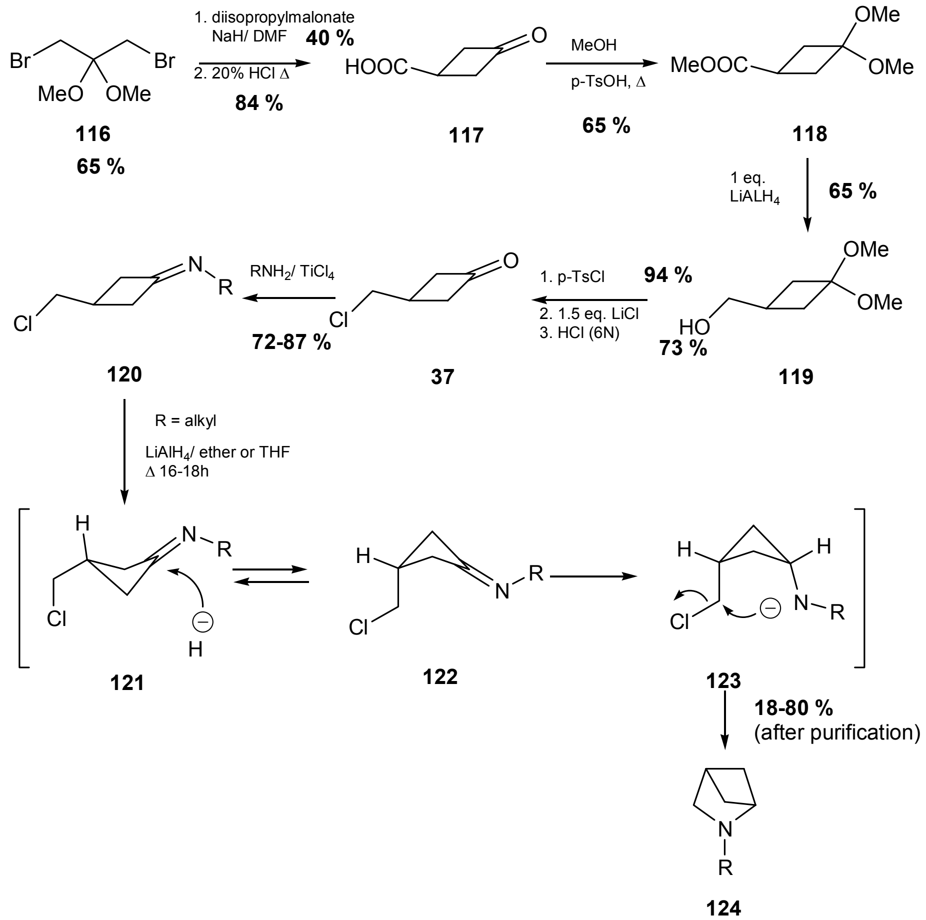
112 **113** **114** **115**

Although being a nice pathway from a chemical point of view, its drawback is that during the electrophilic addition some starting material is not converted to the 2-azabicyclo[2.1.1]hexane skeleton.

3.2.3.3. Through ring closure of a suitable substituted cyclobutyl amine

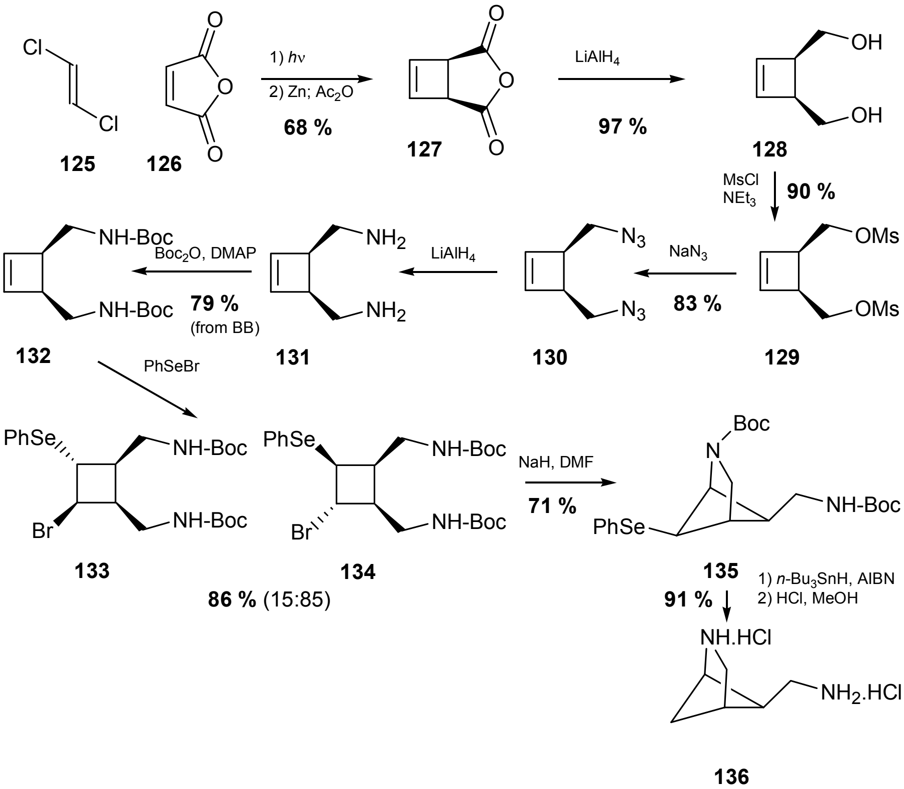
Few syntheses use this mechanism to construct the 2-azabicyclo[2.1.1]hexane skeleton. Goani used it to prepare the natural 2,4-methanoproline (see page 9).[44] To our knowledge, only three research groups applied this reaction sequence.

A promising approach was developed in our laboratory.[37] A suitable γ-haloimine **120** undergoes an intramolecular nucleophilic substitution after it was reduced with hydride. The disadvantage of this procedure is the lack of an easy entry towards 3-halomethylcyclobutanones. The base induced cyclocondensation of 1,3-dibromo-2,2-dimethoxypropane **116** with diisopropyl malonate gave after hydrolysis 3-oxocyclobutane-1-carboxylic acid **117**. This cyclobutanone was subsequently esterified and acetalysed to **118**.

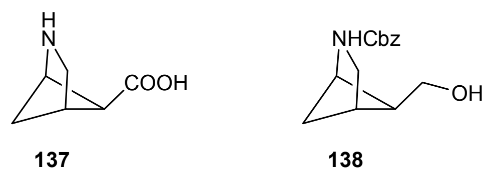


After reduction of **118**, the alcohol **119** is obtained and further derivatised to the 3-(chloromethyl)cyclobutanone **37**. Conversion of the carbonyl group to the corresponding imine with Ti(IV)Cl gave the γ-chloroimines **120**. These γ-chloroimines cyclised after reduction with $LiAlH_4$ to the 2-alkyl-2-azabicyclo[2.1.1]hexanes **124**. No other nucleophiles could be evaluated because of the multi-step sequence to prepare the 3-(chloromethyl)cyclobutanone **37**.

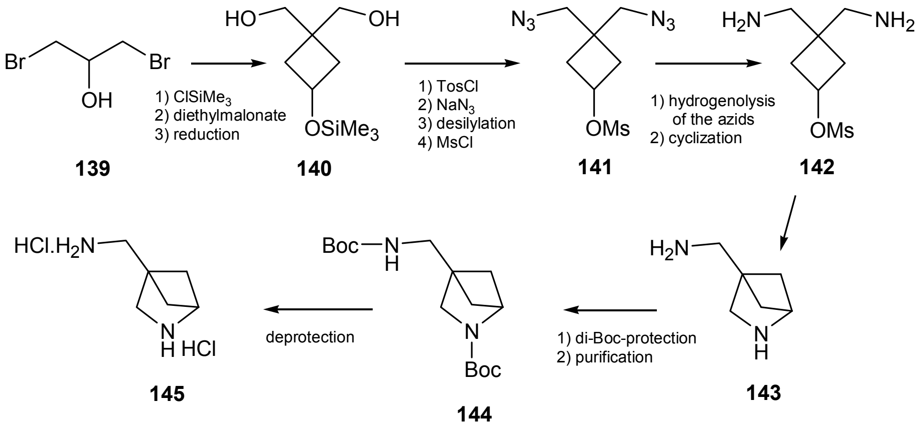
Recently, Huet described the synthesis of the 2-azabicyclo[2.1.1]hexane skeleton starting from *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride **127**. [70]



By means of a lengthy pathway, his research group was able to synthesise 5-substituted 2-azabicyclo[2.1.1]hexanes such as **136**, **137** and **138**. In structure **135** a large four bond coupling of 6.7 Hz between the two bridgehead protons was detected. This was in agreement with the previously reported coupling constants in 2-oxabicyclo[2.1.1]hexanes[67,69] and 2-azabicyclo[2.1.1]hexanes.[37]

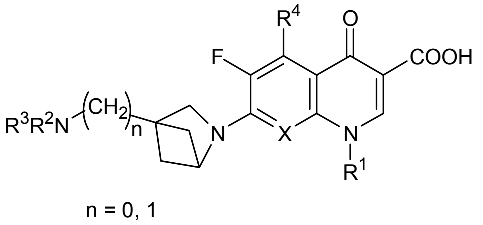


The following patented procedure describes the synthesis of the 2-azabicyclo[2.1.1]hexane **145** used in the synthesis of quinolone carboxylic acid derivatives **146** or **147.** Both derivatives are useful as antibacterials.[81]

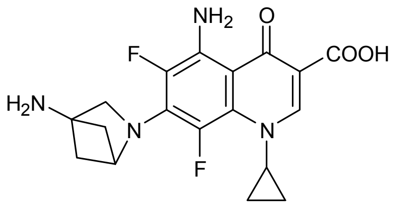


139 **140** **141** **142** **143** **144** **145**

It is important to note that incorporating 2-azabicyclo[2.1.1]hexane skeletons in specific cases improves the biological activity.



146

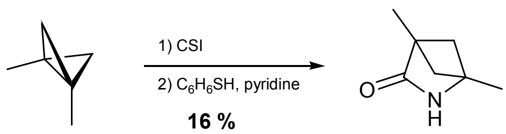


147

3.2.4. Entry to 2-azabicyclo[2.1.1]hexan-3-one

The 2-azabicyclo[2.1.1]hexane skeleton is very constrained but stable. Extra strain can be introduced in the ring when an sp^2 C-atom is present such as in the 2-azabicyclo[2.1.1]hexan-3-one skeleton. Such compounds can be prepared, but are sensitive for nucleophilic ring opening. Only two articles report such compounds.

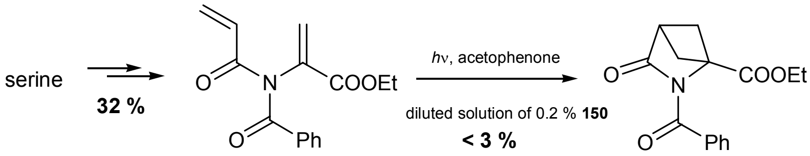
In 1971 the constrained 1,3-dimethylbicyclo[1.1.0]butane **148** was treated with chlorosulfonyl isocyanide (CSI) and led to the isolation of lactam **149**.[82] Although, the yield was very low (16 %), the structure could be unambiguously assigned.



148 **149**

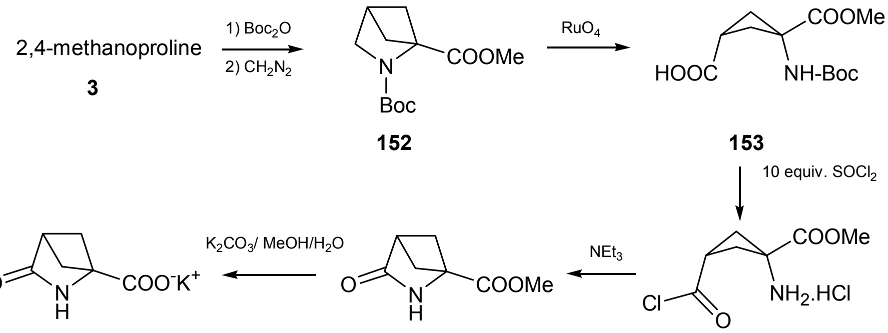
Hughes evaluated two different pathways.[16] In the first, a light induced [2+2]-cycloaddition was used as a key step. The diene **150**, which was prepared from serine, could be cyclised to the 2-

azabicyclo[2.1.1]hexan-3-one skeleton but the yield was very low. This compound **151** was isolated with a yield of less than 3 % and illustrates the drawback of light induced [2+2]-cycloaddition reactions to construct such a skeleton.



150 **151**

A much more diluted solution of **150** (0.2 %) was used since this compound is very susceptible to polymerization under irradiation conditions. Diluting the solution even more (<0.2 %) and adding the diene **150** to a large amount of solvent improved the yield by up to 40 %. The authors noted, this was impractical; therefore they also evaluated the oxidation of 2,4-methanoproline.



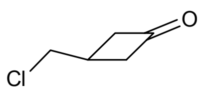
3 **152** **153** **156** **155** **154**

Oxidation of the protected 2,4-methanoproline **152** with RuO_4 resulted in the acid **153** with 66 % yield. The limiting factor of this reaction is the reaction time; it took up to 3 to 4 weeks for the reaction to reach completion. The carbamate **153** was treated with thionyl chloride to obtain the acid chloride **154.** This compound could subsequently be ring closed to the corresponding lactam **155** upon treatment with triethyl amine. Hydrolysing **155** to the acid **156** was successful, but both **155** and **156** proved to be very susceptible for nucleophilic ring opening.

3.3. Synthesis of 3-substituted cyclobutanones and related compounds

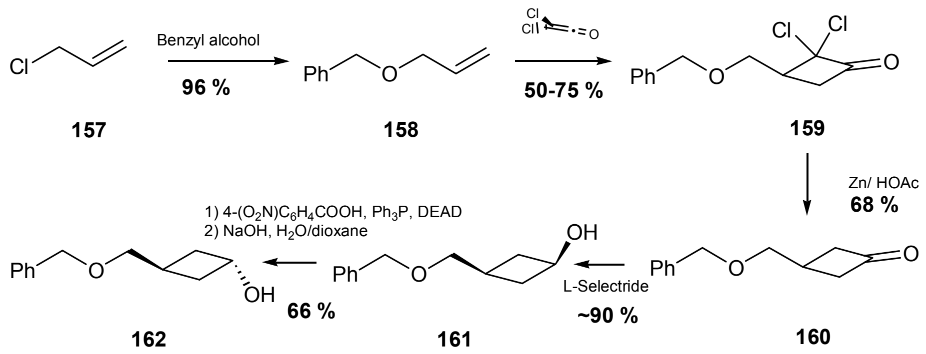
3.3.1. Entry to 3-substituted cyclobutanones

One of the goals of this dissertation is the development of new pathways leading to 3-(chloromethyl)cyclobutanone **37**. Until now only one entry was developed

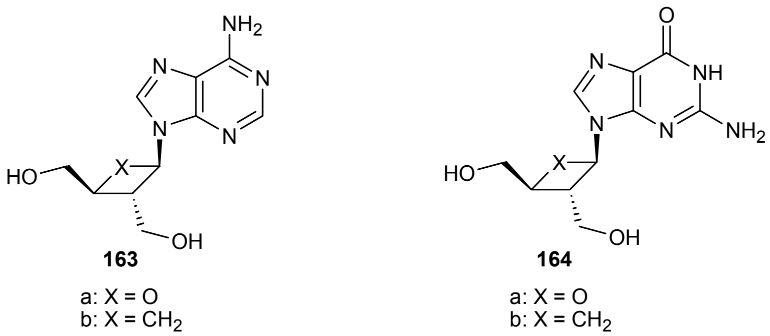


37

in our laboratory, through a multi-step sequence with an overall yield of 6% (see: Entry to the 2-azabicyclo[2.1.1]hexane skeleton through ring closure of a suitable substituted cyclobutyl amine).[37] In view of a new entry to 3-(chloromethyl)cyclobutanone **37** the cyclobutanone **160** could be chosen as starting material.



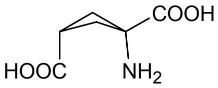
A [2+2]-cycloaddition was performed on allylbenzyl ether **158**. This leads to the cyclobutanone **159** in 50-75% yield depending on the reaction conditions used.[83,84] The two geminal halogen atoms were radically removed using zinc in acetic acid (yield = 68 %). The ketone was reduced using L-selectide in 90 % yield. Mainly the *cis*-isomer was obtained and this was converted to the *trans*-isomer **162** using the Mitsunobu protocol. The alcohol **162** was coupled to adenine, guanine,[83] uracil, thymine and cytosine[84] to prepare analogues **163** of the naturally occurring nucleoside. This compound exhibits both antiviral and antitumor activities. Also oxetanocin G **164** has been found to exhibit antiviral activities.[83]



The observed biological activity of the nucleoside analogues **163a** and **164a** stimulated organic chemists to undertake the synthesis of the corresponding carbocyclic analogues **163b** and **164b**. The enantiomerically pure guanine **164b** was found to have a very high *in vitro* activity against herpes simplex virus types 1 and 2.[85] Other cyclobutane derivatives have been prepared as precursor of cyclobutane carbocyclic nucleosides.[86]

3.3.2. Entry to cyclobutane amino acids and derivatives

Conformationally constrained amino acids have been an important focus of both synthetic and medicinal chemistry, particularly as they are useful for the design of novel peptides. Rigidified cyclic amino acids have also played an important role in drug design and drug development.[87,88]



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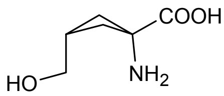
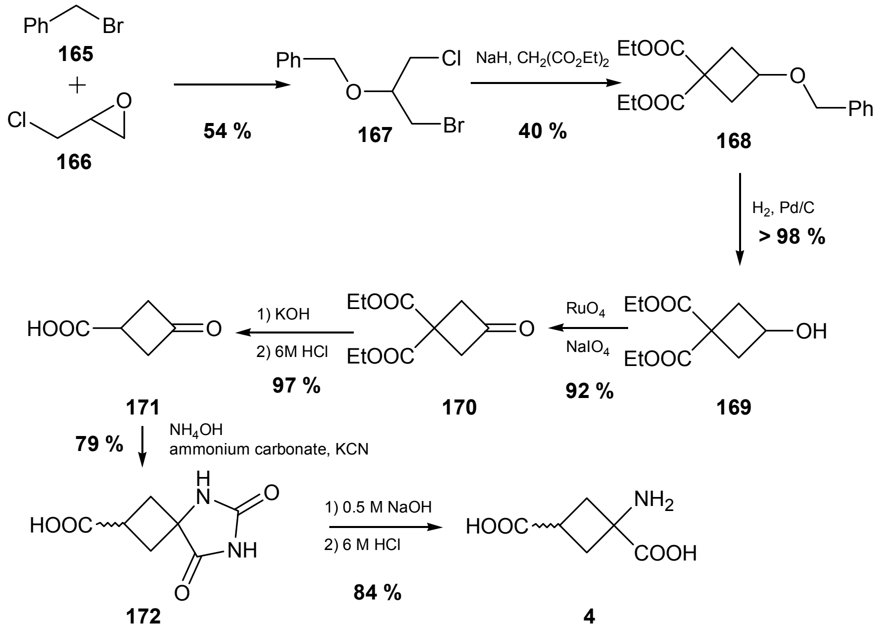


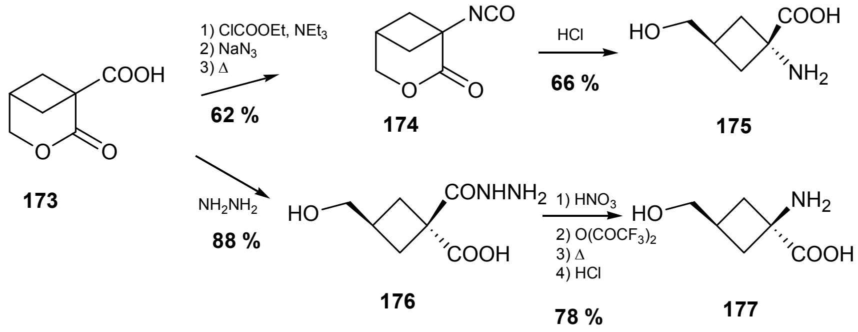
5

Next to 2,4-methanoproline **3**, 2,4-methanoglutamic acid **4** and *cis*-1-amino-3-hydroxymethylcyclobutane-1-carboxylic acid[14] **5** were also isolated from *Ateleia Herbert-smithii Pittier*. Some procedures are available to prepare the cyclobutane amino acids **4** and **5**. One of the possible schemes to prepare the 2,4-methanoglutamic acid **4** (two isomers) is described below.[89] The cyclobutane derivative **168** was prepared from epichlorohydrine in a two step procedure. However, the yield for the formation of the 4-membered ring was low (40%).[90] This compound was subsequently hydrogenated and oxidised to the cyclobutanone **170**.[91]



Hydrolysis of the ester moieties in basic medium and decarboxylation under acidic conditions gave the 3-oxocyclobutanecarboxylic acid **171**. The keto-function was subsequently converted to the hydantoin **172** which after hydrolysis gave the desired 2,4-methanoglutamic acid **4** as a mixture of isomers.

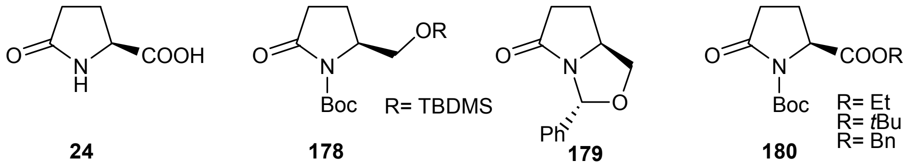
The *cis*- and *trans*-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid **5** were prepared from the bicyclic 3-oxabicyclo[3.1.1]heptan-2-one-1-carboxylic acid **173**.[92,178]



173 174 175 176 177

3.4. Directing the alkylation on the pyroglutamate ring

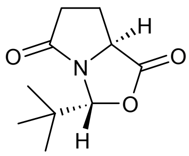
One of the starting materials which was evaluated is L-pyroglutamic acid **24**. This chiral natural product is very versatile since the 2, 4 and 5 position are activated. However, to use pyroglutamic acid as a chiral building block,[93] a great deal of research was performed to protect the acid group in a suitable way. This should prevent isomerisation of the chiral centre during alkylation at the 2-position. In most cases it was necessary to reduce the acid group to the corresponding alcohol[94] and to protect the alcohol with sterically hindered groups (**178**).[95]



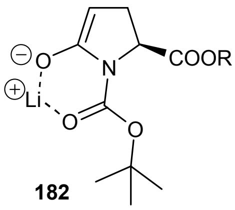
24 178 179 180

Another possibility is to protect the alcohol and the N-atom in an N,O-acetal.[96] Recent research however proved that the protected pyroglutamate **180** could be alkylated selectively at the 4-position without isomerisation of the already present chiral centre.[97]

Enantiospecific alkylations at the 2-position can also be performed on the bicyclic compound **181** prepared by condensation of pyroglutamic acid with 2,2-dimethylpropionaldehyde.[98] Deprotonation with LiHMDS and reaction with electrophiles gave chiral α-substituted pyroglutamate derivatives by self reproduction of the chirality.

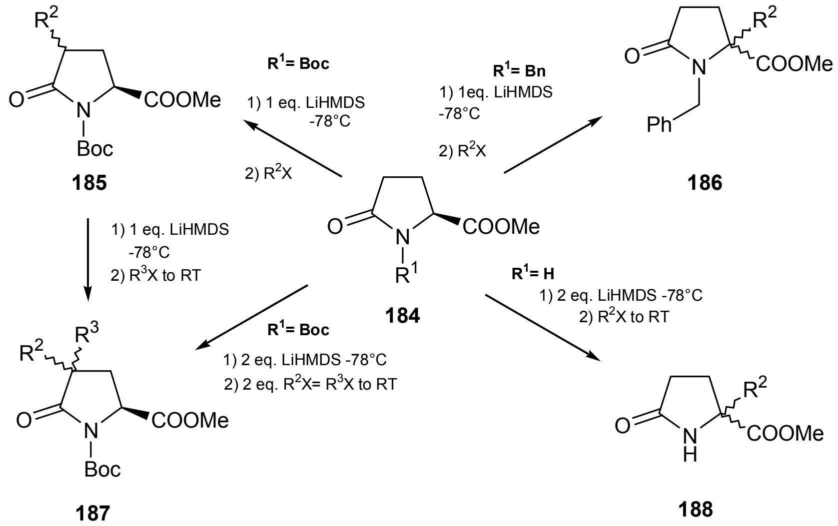

181

Not only the transformation of the acid group is important but the choice of the N-protecting group is of major importance to direct the selectivity of the alkylation. A study concerning the N-protecting group (Me_2t-BuSi, $PhCH_2OCO$, t-BuOCO= Boc) revealed that a t-butoxycarbonyl group was the best group to perform selective alkylations at the 4-position.[97d] Lithiumhexamethyldisilazide (LiHMDS) proved to be the most


182

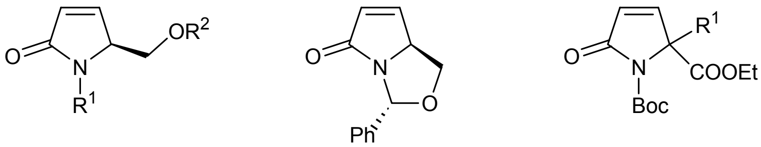
suitable base because the enol is selectively stabilised by the lithium cation in a 6-membered ring (**182**; if the N-protecting group is a carbamate).[99] Ezquerra et al. described a broad range of electrophiles that can be introduced at the 4-position determining the ratio of diastereoisomers.[97a] NOE-experiments showed that the introduced group was mainly *trans* to the ester function at C2. Only in the case of a benzyl group, the *trans* isomer was formed diastereoselectively. In general, the yields were rather good, but the use of propyl or methyl iodide gave yields lower than 10%. It was found that only the sterical hindrance of the electrophile determines the ratio of diastereoisomers. Double alkylation at the 4-position with the same electrophile can be performed in a one or two step sequence.[97c] In both cases no alkylation at the two position was found. Generally the yield of the one step procedure was higher than the two step procedure. An important observation is that the first alkylation proceeds at -78°C but that the second one takes place at room temperature. When using different electrophiles, the electrophile that is introduced last determines the ratio of diastereoisomers.

In the case of a N-benzyl protecting group, no extra stabilisation of the N-substituent exists and the alkylation proceeds selectively at the 2-position with racemisation of the chiral centre present.[99]



Recent investigation revealed that it was not necessary to protect the N-group to achieve alkylation at the 2-position. Methyl pyroglutamate **184** (R= H) can be alkylated at the 2-position using 2 equivalents of base.[100]

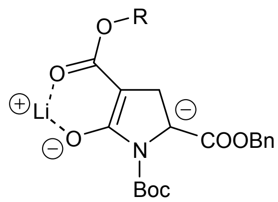
Alkylation at the 3 position can be achieved by Michael addition to 3,4-didehydropyroglutaminol derivatives **189**,[101] **190**[102] or on the pyroglutamate **191**.[100] Nucleophiles can be added at the 5-position (A_N on the amide) leading to ring opening of the lactam ring.[103]



189 **190** **191**

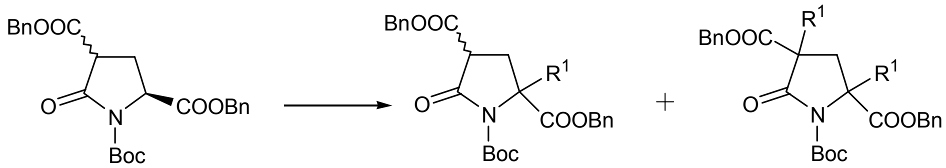
After partial reduction of the amide to the hemi-aminal, nucleophiles can be introduced at the 5-position without ring opening.[104]

Research in our own laboratory, led to another interesting reaction.[112] An alkoxycarbonyl group was introduced at the 4-position of the pyroglutamate **180** (R= Bn) using the corresponding alkyl chloroformate as electrophile. The goal was to introduce a chloromethyl group at the same position. Therefore, the alkoxycarbonyl group was introduced first since direct alkylation with



192 R= Me R= Bn

chloroiodomethane did not succeed. First introducing an activating group should facilitate alkylation and avoid elimination of chloride of the chloromethyl group. The reaction was evaluated with LiHMDS as base but unfortunately no alkylation was observed using only one equivalent of this base. The use of 2 or 3 equivalents however, led to selective alkylation at the 2-position (see Results and discussion). The change of selectivity could be explained by the intermediate **192**. The formed enolate at the 4-position is trapped or strongly complexed in a 6-membered ring. Therefore, the anion is not reactive towards electrophiles under the conditions used. The anion at the 2-position however, can react with the electrophile and produces the end product. The reaction was evaluated with several electrophiles and only in the case of benzylbromide and allylbromide, 4% of dialkylated products could be retrieved.

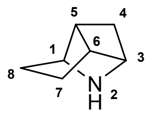


193 **194** **195**

Table 2: Yield of compounds **194** and **195** obtained after alkylation of **193**

R^1=	Yield **194**	Ratio of diastereoisomers	R^1=	Yield **195**
-CH_2Cl	47 %	(57/43)		
-CH_2CH_3	60 %	(70/30)		
-$CH_2CH{=}CH_2$	60 %	(60/40)	-$CH_2CH{=}CH_2$	4 %
-CH_2Ph	41 %	(71/29)	-CH_2Ph	4 %
-p-CH_2PhCl	74 %	(63/37)		

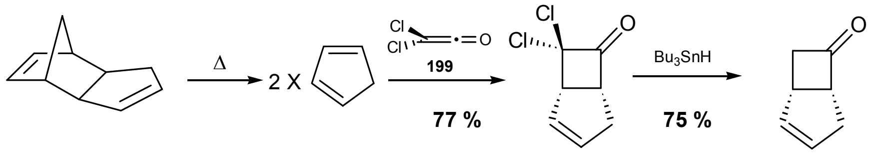
3.5. Entry to tricyclo[3.3.0.0^{3,6}]octanes



2-azatricyclo[3.3.0.0^{3,6}]octane

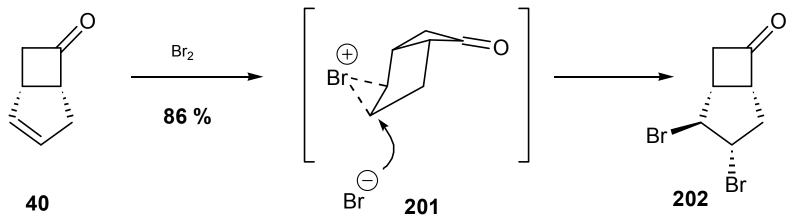
196

Compounds containing the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton **196** are, to the best of our knowledge, not described in the literature. The corresponding C-analogue (tricyclo[3.3.0.0^{2,7}]octane), on the other hand, has been prepared using a [2+2]-light induced cycloaddition reaction or by ring closure of an appropriate camphor derivative.[105] One of our goals is to prepare the 2-azatricyclo[3.3.0.0^{3,6}]hexane skeleton starting from the bicyclic ketone **40**. This ketone is very easy to prepare on large scale.[106] Cyclopentadiene **198**, prepared through retro-Diels Alder reaction of dicyclopentadiene **197**, reacts with dichloroketene (this dichloroketene was generated from dichloroacetylchloride).



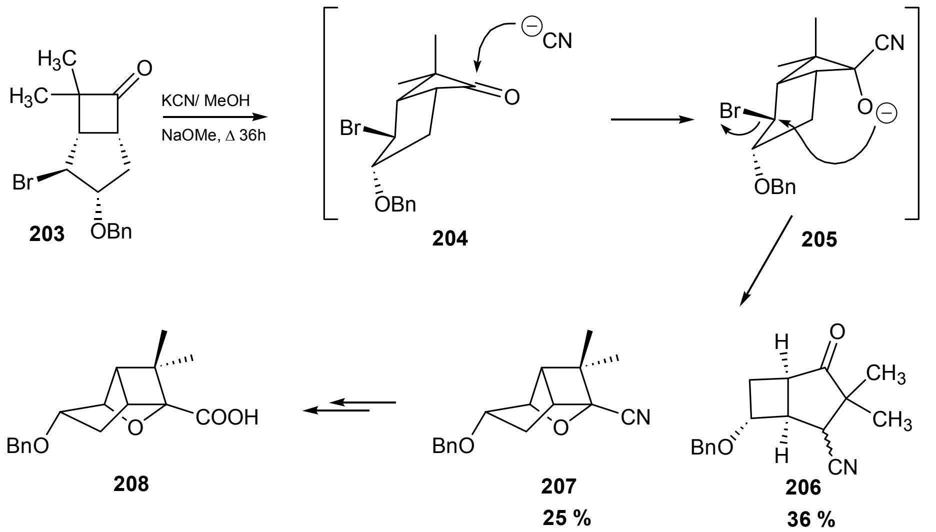
197 **198** **200** **40**

The geminal chlorine atoms can be removed radically and resulting in the bicyclic ketone **40** in 75% yield. This ketone has been used for the synthesis of Prostaglandin-F$_{2\alpha}$.[107] The double bond of the obtained cyclobutanone can be brominated leading to the dibromo-compound **202**. This bromination reaction is completely diastereoselective due to the exo attack of bromine on the double bond and subsequent regioselective opening of the resulting bromonium ion by attack of bromide at the less hindered carbon position (**201**).[108]



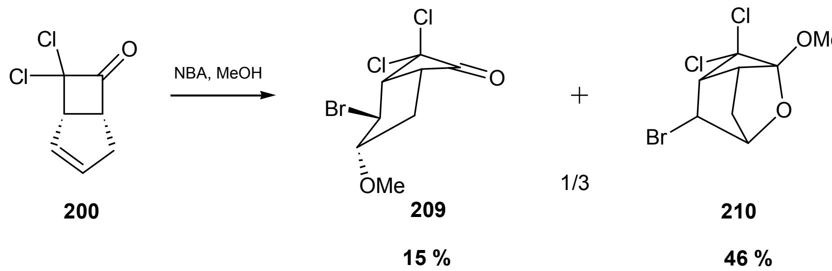
40 **201** **202**

The 2-oxatricyclo[3.3.0.0^{3,6}]octane skeleton was formed by adding potassium cyanide to the cyclobutanone **203**, which cyclised in 25 % yield to the tricyclic compound **207** together with the rearranged product **206** (yield = 36%).[109]



This reaction illustrates that the constrained 2-oxatricyclo[3.3.0.0^{3,6}]octane skeleton can be formed relatively easily, despite the side reaction.

The formation of a 2-oxatricyclo[3.2.1.0^{3,6}]octane **210** was observed upon bromination of ketone **200** by *N*-bromoacetamide (NBA) in methanol.[108,110,111] A mixture of compounds **209** and **210** was obtained in a 1/3 ratio. After purification, these compounds were isolated with a yield of 15% and 46%, respectively. During the reaction, methanol added to the keto-function with formation of a hemi-acetal. This functional group subsequently opens the bromonium ion with formation of **210**.

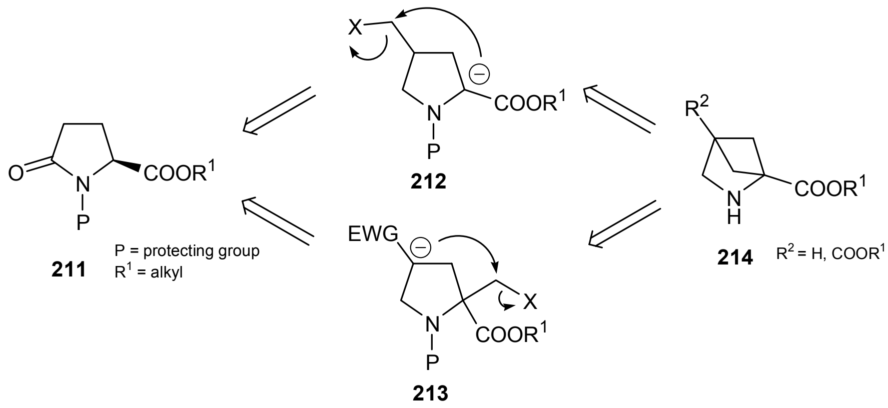


4. Results and Discussion

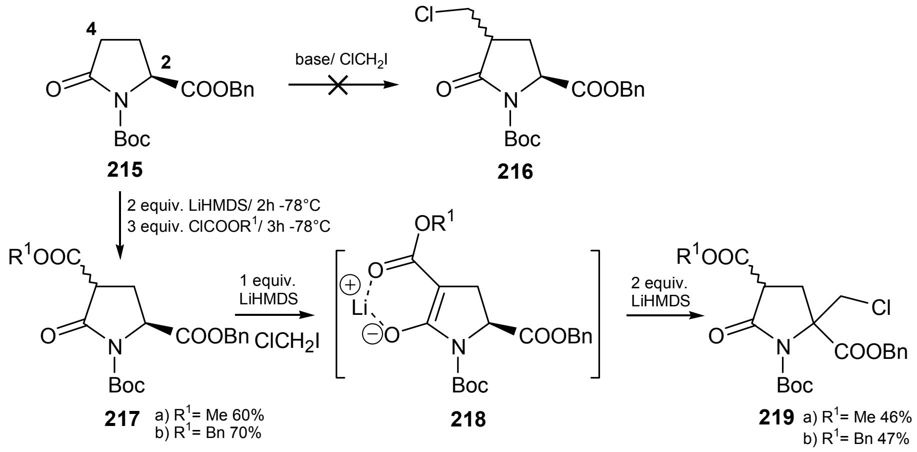
4.1. Entry from pyroglutamate derivatives

4.1.1. Selective alkylations at the 2- and 4-postion of the pyroglutamate ring

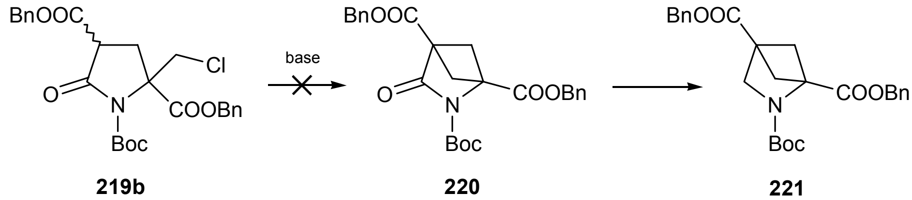
In the first two routes, attempts will be undertaken to construct the 2-azabicyclo[2.1.1]hexane skeleton by formation of a 4-membered ring in an existing 5-membered pyrrolidine ring. The protected pyroglutamate **211** will be used as starting material to prepare suitable pyrrolidines **212** and **213**.



Many reactions using pyroglutamic acid as building block have already been described in the literature, but seldom has a halogen group been incorporated and further used to synthesise bicyclic structures. The introduction of a halogen group opens various possibilities for further transformations and therefore the ring closure between C2 and an halomethyl group at C4 (or *vice versa*) was investigated in order to construct bicyclic constrained analogues of glutamic acid.
From previous research in our laboratory,[112] it was found that direct alkylation at the 4-position with choroiodomethane was unsuccessful.

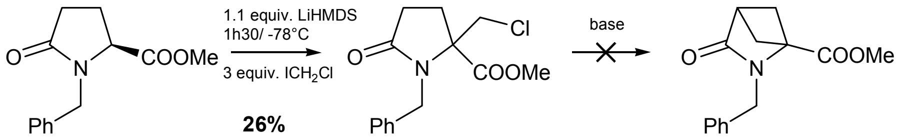


To overcome this problem an alkoxycarbonyl group was first introduced at the 4-position to activate this position and to avoid dehydrohalogenation of the chloromethyl group. Using 1 equivalent of LiHMDS as base, it was impossible to alkylate compound **217** and introduce an alkyl group at the 4-position. Only when an excess of base was used (2 or 3 equivalents LiHMDS), a chloromethyl group was incorporated, but rather unexpectedly, at the 2-position. This is strange since the 4-position is more activated than the 2-position. An explanation can be found in the stabilisation of the first formed anion **218** in a 6-membered ring. The stabilisation makes the anion unreactive towards the electrophile under the applied reaction conditions. The second anion is subsequently formed at the 2-position and is reactive enough towards the electrophile. More details concerning this reaction can be found in the literature.[113]



Once this chloromethyl group was introduced, several attempts were made to close this molecule to the 4-position. This would lead to the 2-azabicyclo[2.1.1]hexane skeleton after reduction of the amide moiety. In all attempts the product broke down or the starting material was recovered.

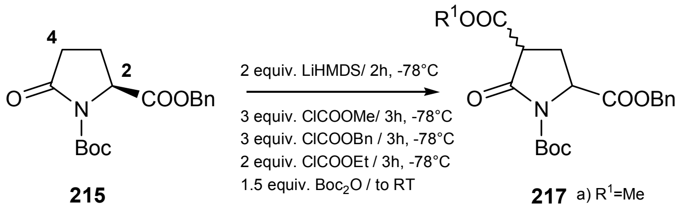
A chloromethyl group was also introduced at the 2-position by alkylation of methyl N-benzylpyroglutamate **222**[112,114] using chloroiodomethane, although the yield was very low (26%). When compound **223** was treated with bases such as LDA, LiHMDS, NaH or KH, no reaction was observed and the starting material was recovered totally.



222 **223** **224**

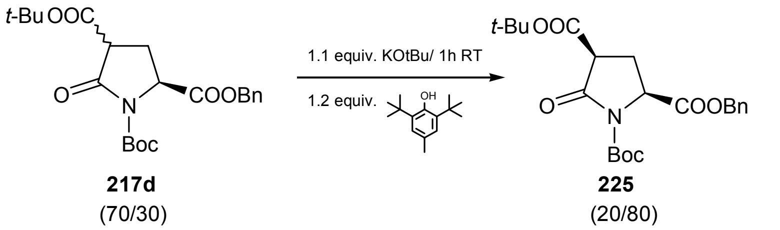
It has been described in literature that methyl pyroglutamate can be alkylated, without N-protecting group, using 2 equivalents of base.[100] This procedure was evaluated using chloroiodomethane as electrophile but no reaction was observed and the starting material was recovered.

Because of our interest in pyroglutamic acid as chiral building block, this type of chemistry was further developed. One of the problems that arose, was the purification of the benzyl 4-(alkoxycarbonyl)-1-(t-butoxycarbonyl)pyroglutamate **217b**. It had to be purified by flash chromatography which is not convenient to use on large scale. Therefore, some derivatives were prepared to find a crystalline one. The benzyl N-t-butoxycarbonyl pyroglutamate was alkylated using ethyl chloroformate or di-t-butoxydicarbonate as electrophile to introduce an ethoxy- or t-butoxycarbonyl group at the 4-position. The compound containing an ethoxycarbonyl group **217c** was a viscous oil, but when the t-butoxycarbonyl group was introduced a crystalline product was obtained. This compound **217d** can now be synthesised on a large scale and was purified by crystallisation.

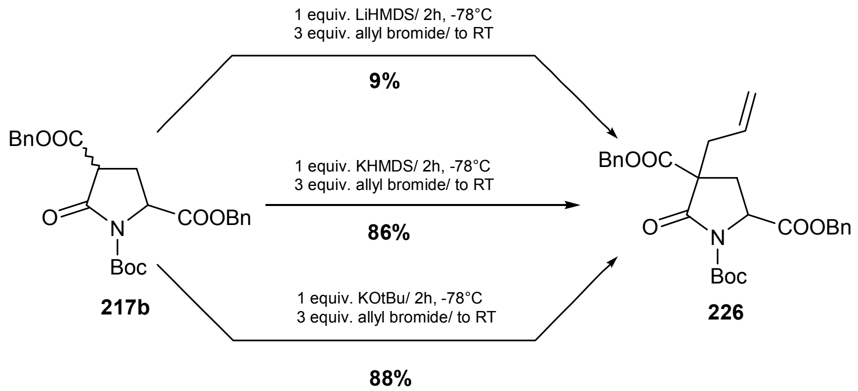


215 **217** a) R^1=Me 60% oil
b) R^1=Bn 70% oil
c) R^1= Et 72% oil
d) R^1= *t*-Butyl 77% Mp.= 84-86.5°C

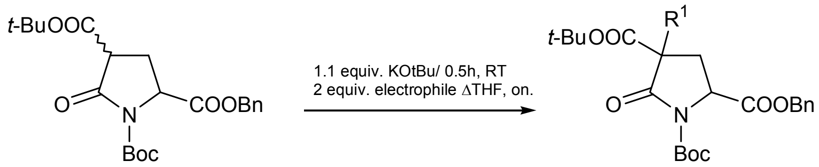
The main differences with the other electrophiles were that only 1.5 equivalents of electrophile and 2 equivalents of base (LiHMDS) were used and that the reaction was allowed to heat to room temperature overnight. A smaller excess of electrophile could be used since traces of the remaining starting material could be removed during crystallisation. The reaction was allowed to warm up to room temperature because di-t-butoxydicarbonate is a rather poor electrophile and higher temperatures were needed to achieve a good conversion. Using the other reaction conditions (-78°C), it was necessary to use a larger excess of electrophile since the starting material **215** was difficult to remove by column chromatography. On the other hand 2 equivalents of base were used which appears strange at first sight. Using only 1 equiv. of base (LiHMDS), led to a low yield, almost half of the yield stated above. The explanation for this low yield can be attributed to the deprotonation of the formed end product **217**. The proton at the 4-position is more acidic than the CH_2 (C4) of the remaining starting material **215**. Therefore, 1 equivalent of base will give a maximum yield of 50%. The 2-benzyl 1,4-di-t-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate **217d** was obtained as a mixture of diastereoisomers (*trans/cis* 70/30). In the major diastereoisomer the ester functions at the 2 and the 4-position are *trans*. This was proven by deprotonating **217d** at the 4-position and quenching the reaction with a very hindered proton source. The diastereoisomer ratio shifts from 70/30 (*trans/cis*) to 20/80 (*trans/cis*). Using a hindered phenol, the molecule is protonated from the least-hindered side of the molecule leading mainly to the *cis*-isomer.



As can be seen from the scheme, the weaker base KOtBu was used to deprotonate the 4-position. When LiHMDS was used, no alkylation could be performed with less reactive electrophiles. The main reason is the strong complexation of the lithium kation in the 6-membered ring. When the lithium counter ion was replaced with a potassium counter ion, the alkylation proceeds with very good yield.[113] The alkylation was evaluated using allyl bromide, which is a very good electrophile and LiHMDS, KHMDS and KOtBu as base. From the same scheme it can be concluded that the bigger potassium ion does not stabilise the anion as much as lithium does, leading to high yields of the end product. It was also unnecessary to use the strong and expensive base KHMDS and the yields were as good when KOtBu was used as base.



The possibility to alkylate at the 4-position was further investigated using different electrophiles. The reaction conditions were also optimised. It seemed unnecessary to perform the reaction at low temperature and the yield was improved when the reaction mixture was heated under reflux overnight.



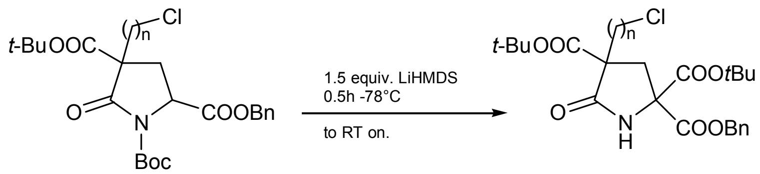
217d **227a-g**

Table 3: Alkylation on **217d**, leading to C4-substituted pyroglutamates **227a-g**

R^1=	Electrophile	Yield
a) $-CH_2CH{=}CH_2$	$BrCH_2CH{=}CH_2$	81 %
b) $-CH_3$	ICH_3	53 %
c) $-CH_2Cl$	ICH_2Cl	58 %
d) $-CH_2CH_2Cl$	$BrCH_2CH_2Cl$	26 %
e) $-CH_2CH_2CH_2Cl$	$BrCH_2CH_2CH_2Cl$	82 %
f) $-CH_2C{=}CH_2CH_2Cl$	$ClCH_2C{=}CH_2CH_2Cl$	60 %
g) -Br	NBS (RT on.)	29 %

Other electrophiles such as diiodomethane and dibromomethane were also evaluated but in the crude product the yield was not more than 10%, so these reaction mixtures were not further purified. Table 3 shows that the yields are moderate to good except for $BrCH_2CH_2Cl$ and NBS.

The idea was to evaluate the ring closure of **227c,d,e,f** by deprotonation at the 2 position. From previous experiments it was already known that constructing a 4-membered ring in the 5-ring would be difficult. When **227c** was treated with LiHMDS, the starting material was completely converted to a new product. Unfortunately this compound was not the desired bicyclic compound but a different reaction took place.

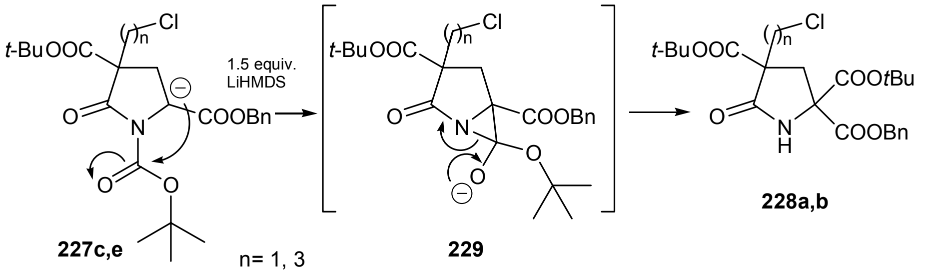


227c,e n= 1,2 **228a,b**

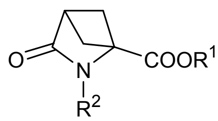
Table 4: Yields of the rearranged products **228a**,**b**

n	R^1=	Yield
n= 1	a) $-CH_2Cl$	61 %
n= 2	b) $-CH_2CH_2CH_2Cl$	64 %

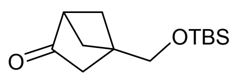
In the H-spectra, the CH proton at the C2-position had disappeared and the remaining CH_2 of the ring was reduced from a ABX-system to a AB-system. All the other groups were still present but did not shift much. A broad singlet appeared at around 6.41 ppm, which is probably the N<u>H</u> proton from the amide. The 2 singlets (each 9H) from the t-butyl groups were still present. After purification of the product (the crude product was almost pure), the ^{13}C-spectra confirmed the assumptions from the H-spectra. The carbonyl (C=O) of the t-butoxycarbonyl group (N-Boc) which is normally around 150 ppm was missing, but two t-butyl groups were present. Taking all this information into account, structure **228a**,**b** was deduced, where the Boc-group migrated from the N-atom to the C2 position.



The mechanism is postulated as follows. The formed anion at the 2-position is unreactive towards the chloromethyl group, but at room temperature the anion is sufficiently reactive to undergo a nucleophilic addition reaction on the adjacent N-Boc group. The bicyclic intermediate formed is not stable and opens again to form **228a**,**b**. This means that migration of the N-protecting group was faster than the formation of a 4-membered ring. Our previous work[112] showed that probably the ring strain and the planar amide bond are the main reasons why the 4-membered ring cannot be formed. The skeleton is however described in literature and these compounds **230a**,**b** are stable.[16] Also the C-analogue **231**[64] and **232**[115] exists and are stable molecules. The construction of a 4-membered ring in an existing 5-membered ring should be possible since some examples of C-analogues are known in literature.[116,117] It was thought that enlarging



230 a) R^1 = H, R^2 = H
b) R^1 = CH_3, R^2 = COC_6H_5



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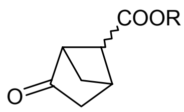


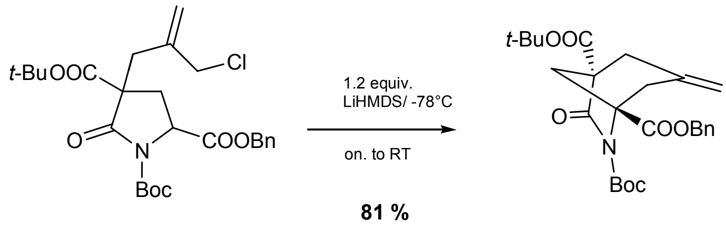
232

the second ring would overcome this problem.

The reaction was evaluated with **228b**, since the chloropropyl group would lead to a 6-membered ring. Again, no ring closure occurred and the Boc group migrated in good yield (64 %).

4.1.2. Synthesis of the 6-azabicyclo[3.2.1]octan-7-one skeleton

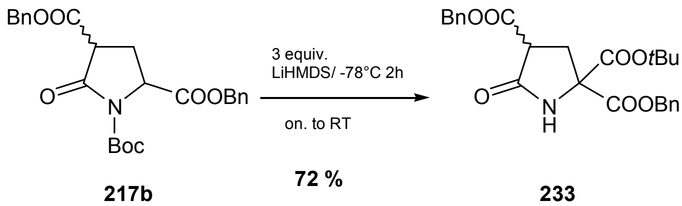
After this experiment we concluded that this migration has to be a rather fast reaction in comparison with the ring closure, so a better electrophile was chosen. Compound **227f** was prepared according to the previously described procedure, using 3-chloro-2-(chloromethyl)-1-propene as electrophile. The chloride at the allylic position would act as a better electrophile facilitating the ring closure. Treating **227f** with 1.2 equivalents of LiHMDS at -78°C and allowing the reaction to warm to room temperature overnight led to the formation of the bicyclic structure **232** in very good yield (81%).



227f **232**

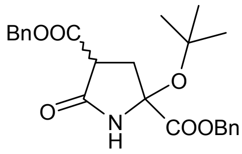
The Boc-group is very often used when working with pyroglutamic acid. Migration of the Boc-group is not known up to now in literature and is an important side reaction which should be taken into account.

During previous work,[112] an analogous side reaction took place. When benzyl 4-(benzyloxycarbonyl)-1-(t-butoxycarbonyl)-pyroglutamate **217b** was treated with an excess of base (3 equiv., LiHMDS) and no electrophile was added, the Boc-group also migrated but at that time insufficient evidence was available to prove the structure. The reaction was reinvestigated and the spectra were analysed.



217b **233**

The main reason why the structure of **233** was uncertain was the presence of only 5 carbonyl groups in the carbon spectrum. Since a mixture of diastereoisomers was obtained, 8 carbonyl groups were expected: 6 from the ester functions and 2 from the amide functions. For this reason structure **234** was proposed at that time but without postulating a mechanism. The mass spectrum



234

gave no extra information since the direct inlet apparatus did not show the molecular ion. The mass spectrum was now collected with an electron spray apparatus and the molecular ion confirmed structure **233**. Extra evidence was found recording the ^{13}C-spectrum in deuterated benzene. This was done to evaluate the ASIS (Aromatic Solvent Induced Shift) on the different carbonyl groups. Indeed, 8 carbonyl groups were present instead of 5, another proof of structure **233** (Figure 2 and 3).

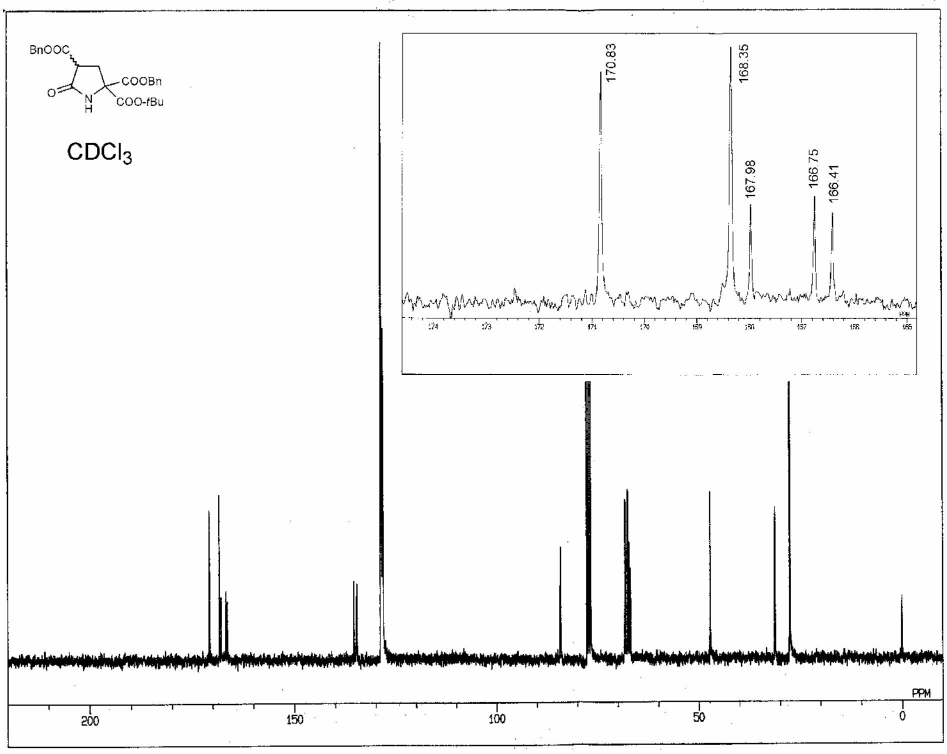


Figure 2: ^{13}C-spectra of compound **233** in $CDCl_3$

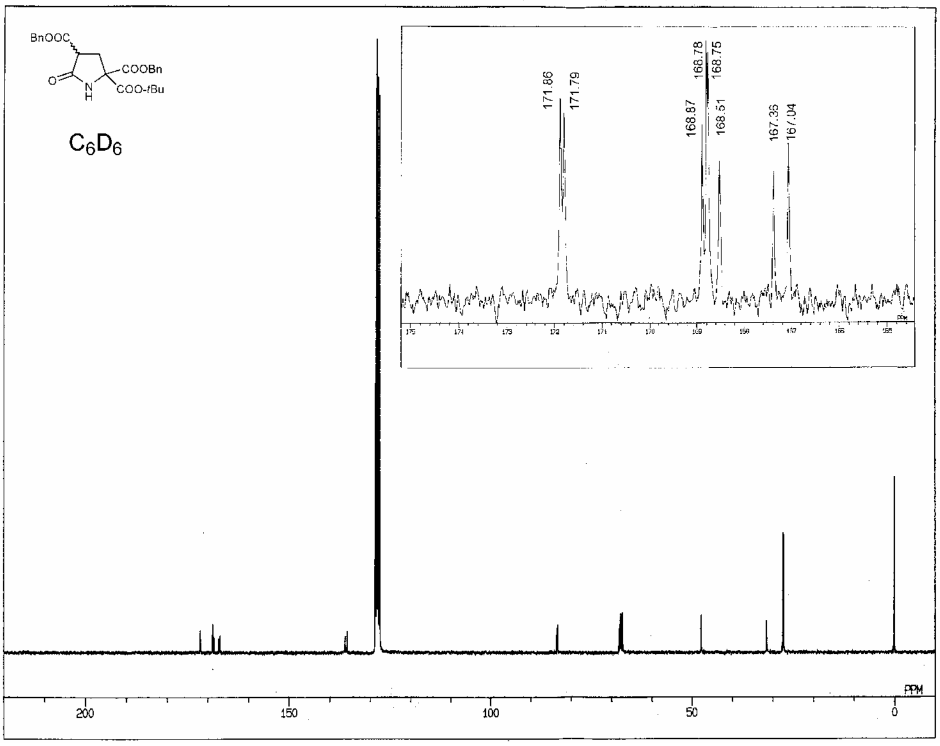
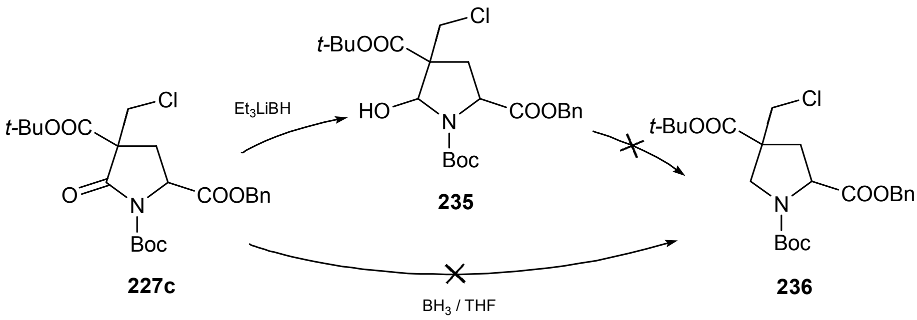


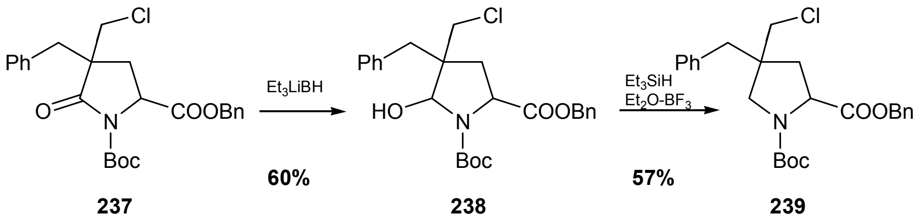
Figure 3: ^{13}C-spectra of compound **233** in C_6D_6

Attempts were undertaken to selectively reduce the amide bond of pyroglutamate **227c** since the amide functionality is limiting the flexibility of the ring, thus reducing the possibility for ring closure.



Several selective methods to reduce the amide function of pyroglutamates are already described in literature.[93,118,119,120,121,122,123,124,125,126] One mild method uses lithium triethylborohydride[118] which reduces the carbonyl group to the hemi-aminal. This hemi-aminal can be further reduced to the amine using triethylsilyl hydride and boron trifluoride. When the reduction to the hemi-aminal was evaluated, the crude reaction mixture was very complex and it was clear that not only reduction of the amide group had occurred. Because of the complexity of the proton spectra, the crude hemi-aminal **235** (3 chiral centra) was further reduced using triethylsilyl hydride. Unfortunately, the reaction mixture was so complex that compound **236** could not be isolated. Another method to reduce the amide bond in one step to the corresponding amine uses borane.[124] This is a mild reductant that is known to selectively reduce amides in the presence of esters and/or carbamates. Again, a complex reaction mixture was obtained and the end product could not be isolated.

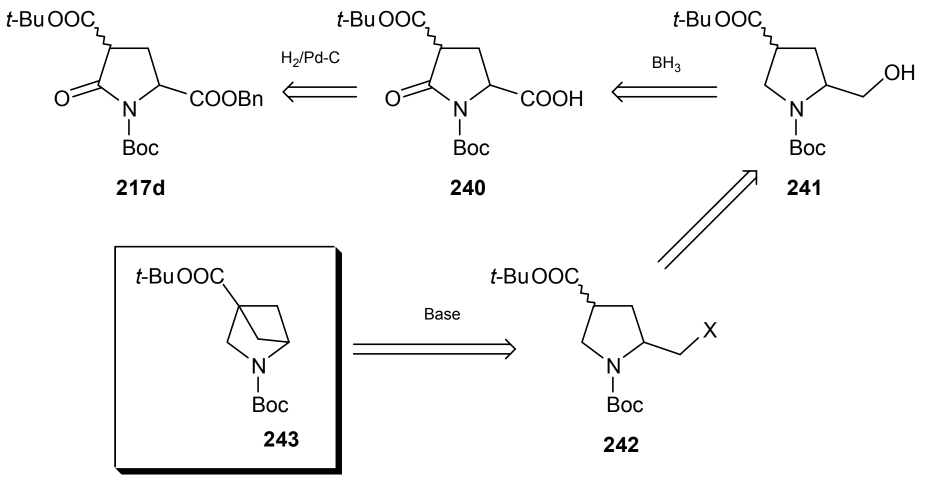
Although the spectra were complex, it looked as if a reduction of the ester group at C4 took place. From our previous work was known that these methods for reduction do work, but in these cases a benzyl group instead of an ester function was present at the C4-position.[112]



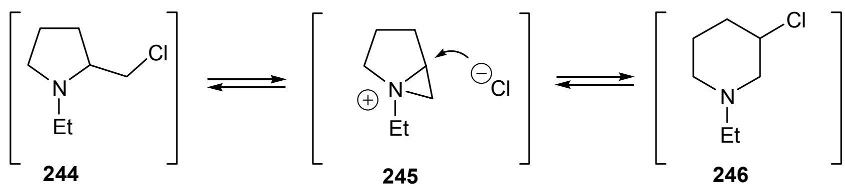
The reduction of the pyroglutamate **237** to the amine **239** was performed in two steps using Et_3LiBH and Et_3SiH (Et_2O-BF_3). The yield was moderate and the disadvantage of this procedure was the purification with flash chromatography. Because the reduction of **227c** gave so many side products it was not further investigated.

4.1.3. Attempted synthesis of the 4-alkoxycarbonyl-2-azabicylo[2.1.1]hexane skeleton

The introduction of a chloromethyl group at the C2-carbon through alkylation of methyl N-benzylpyroglutamate **222** (1.1 equiv. LiHMDS) had a low yield (26%) and thus another strategy was evaluated.

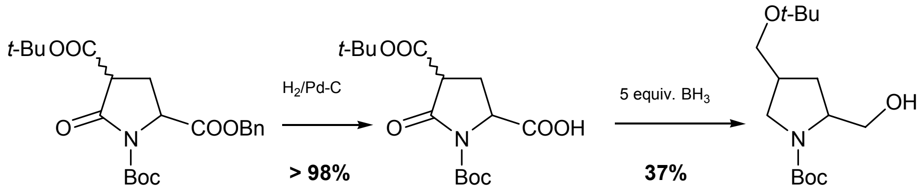


The pyroglutamate **217d** was now used as starting material since this compound could be made on multi-gram scale. It can be prepared in three steps with two crystallisations to purify the intermediates. The aim was to hydrolyse the benzyl ester at C2 to the corresponding acid. This compound **240** would be reduced with borane. Borane is known to reduce the acid function to the alcohol and the amide to the amine without affecting the ester function. The obtained alcohol would then be converted to a better leaving group in order to attempt ring closure to form the 4-alkoxycarbonyl-2-azabicyclo[2.1.1]hexane skeleton (**243**). A Boc-group has to be present on the N-atom of compound **242** to make it less nucleophilic.



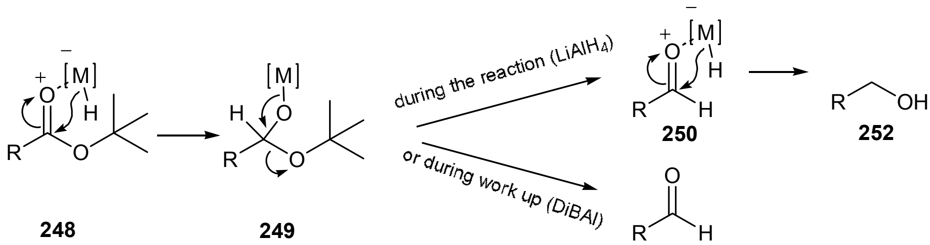
When no electron withdrawing group is present on the N-atom a rearrangement, ring expansion, takes place to a piperidine skeleton.[127,128,129]

The first step proceeded as planned, catalytic hydrogenation indeed selectively deprotected the benzyl ester. No side products were formed and no purification was necessary. The reduction was then evaluated using borane. The literature method[130] mentioned the use of an excess of borane because a part of this reagent complexes with all the O-atoms present in the molecule. For this reason 5 equivalents of borane were used.



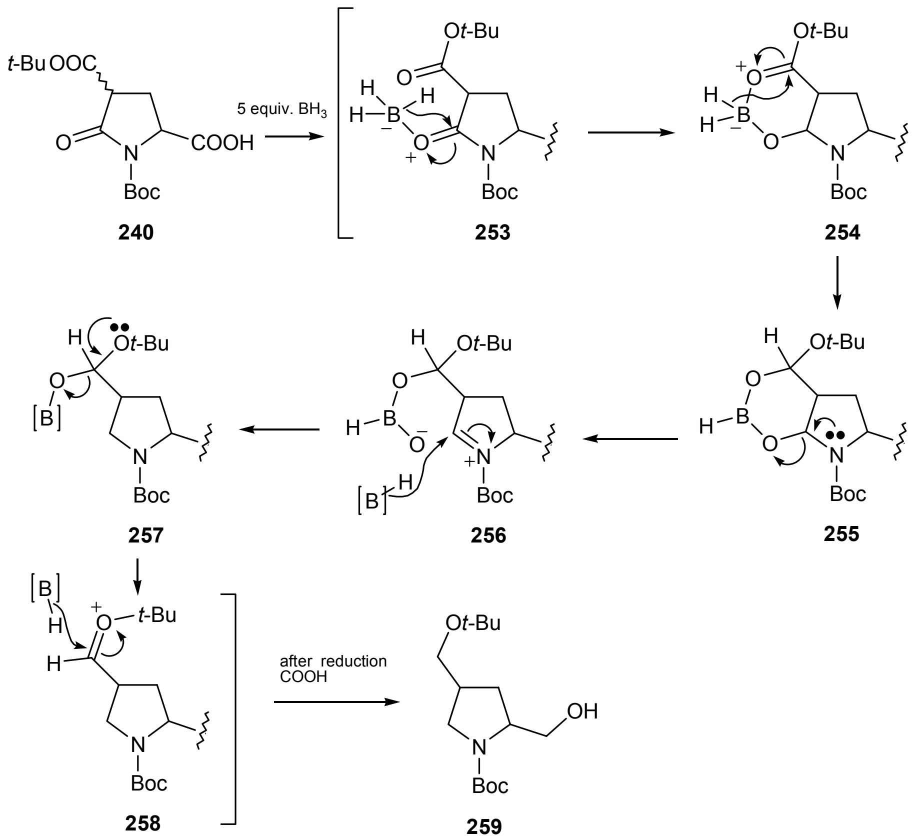
217d 240 247

After performing this reaction, the crude product was purified through column chromatography and a major amount of compound was lost due to the polar nature of **247**. However, an over-reduction took place which was not expected since borane normally does not reduce ester functions. When an ester group is reduced with a hydride reagent, initially a complex **248** between the metal and the carbonyl group is formed. The carbonyl group is then more susceptible for nucleophile attack and hydride is transferred from the metal to the carbonyl group. Depending on which reagent is used, for instance $LiAlH_4$, the alkoxy group is kicked out and an aldehyde is formed in situ which is then further reduced to the corresponding alcohol **252**. In the case of other reagents such as DiBAl, the expulsion of alkoxyde only proceeds during workup and no further reduction of the aldehyde formed takes place.



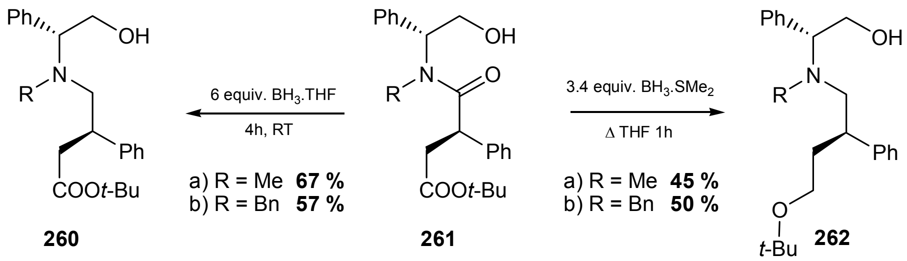
248 249 250 251 252

In our particular case, the t-butyl ether was formed instead of the alcohol. The acid group was reduced via the classical way. A possible mechanism is described in the next scheme: borane complexes with the carbonyl group of the amide bond and because of the strong bond between boron and oxygen, the carbonyl group is more polarised. A hydride is then transferred from borane to the amide. Until this point the reaction proceeds as usual. From the previous work was known that lithium can make a rather stable complex in a 6-membered ring between the amide and the ester group at C4 and probably boron does the same.

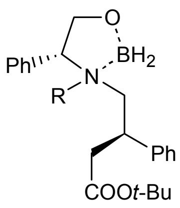


For the same reason described above, a hydride is transferred from borane to the carbonyl group of the ester function. Probably because the O-B bond is so strong, the t-butoxy group is not expelled but the borane ester is cleaved and the remaining group is further reduced to the ether **259**. Unfortunately this reaction did not lead to the desired compound **241**, but still it is an interesting reaction that should be investigated further.

Few literature references are available describing such reductions, but one analogous reaction has been reported.[131]



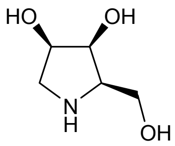
Using 3.4 equivalents of borane-SMe_2, the t-butyl ester of compound **261** was converted to the corresponding ether **262**. The authors proposed the oxazaborolidine **263** as intermediate which could catalyse the reduction of the ester function. Compounds **262a**,**b** were isolated in 45 and 50% yield respectively. Strangely enough, when 6 equiv. of borane-THF were used the amide was reduced but not the t-butyl ester (isolated yield **260** = 57-67%).



263

Another reduction of a t-butyl ester has been described using sodium borohydride and boron trifluoride as reductive reagents.[132]

Alkaloids and synthetic aza-sugars such as **264** that structurally resemble monosaccharides, but where the ring O is replaced by N, display glycosidase inhibitory properties and are of significant importance.



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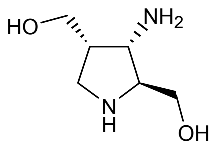

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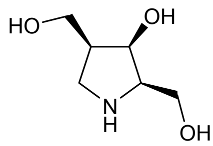
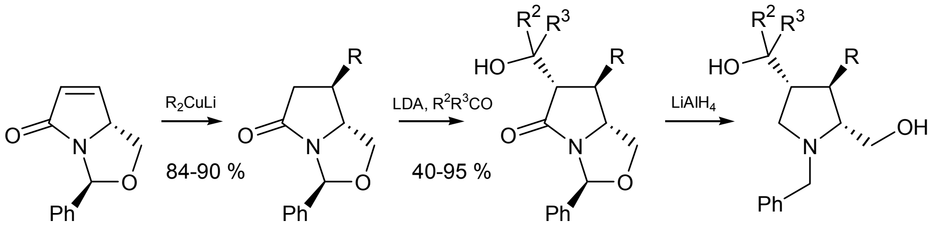


266

They have potential applications in the treatment of diabetes but also for AIDS and chemotherapy of cancer.[133,134] Polyhydroxylated pyrrolidine, piperidine and indolizidine alkaloids have therefore attracted considerable attention due to their ability to inhibit glycosidases.[135,136] Analogues such as compound **265** and **266** were tested for their potential α-glycosidase activity.

Some compounds such as **270** were also derived from pyroglutamic acid (D-form), but were synthesised using a different pathway. Pyroglutamic acid was first transformed to **267** and subsequently alkylated at the 3 and the 4 position. After reduction using lithium aluminium hydride, the pyrrolidines **270** were obtained enantioselectively.[137]

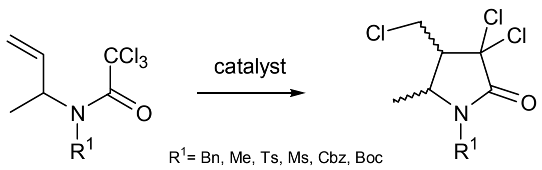


267 **268** **269** **270**

4.2. Entry to 4-(halomethyl)-2-pyrrolidinecarboxylates

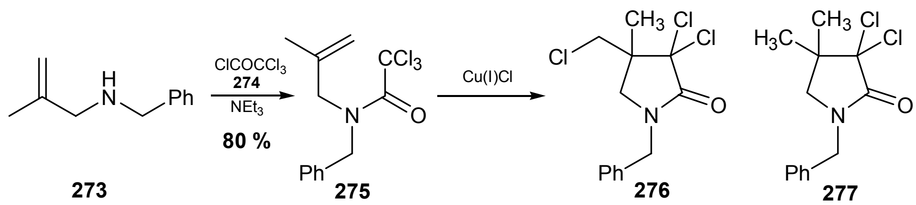
4.2.1. Using the Kharasch reaction

One of the possible reactions to prepare 4-(chloromethyl)-2-pyrrolidinones is the Kharasch reaction. The general reaction mechanism is depicted below.[138] The cyclization of the N-benzyl N-allyltrichloroacetamide **271** is catalysed by transition metals and results in the formation of 4-(chloromethyl)-2-pyrrolidinones **272**.[139]



271 **272**

To avoid dehydrohalogenation at the chloromethyl group attempts were made to prepare a derivative which has a quaternary C4 centre such as **276**. To be able to use such a 4-(chloromethyl)-2-pyrrolidinone in the synthesis to 2-azabicyclo[2.1.1]hexanes, the geminal chloride atoms have to be removed later on and the amide should be converted to an amino nitrile.



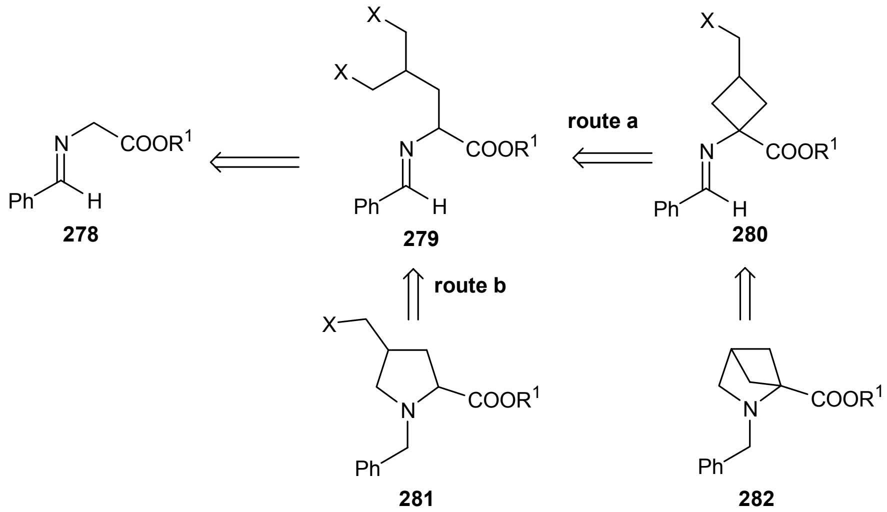
273 **275** **276** **277**

45 %

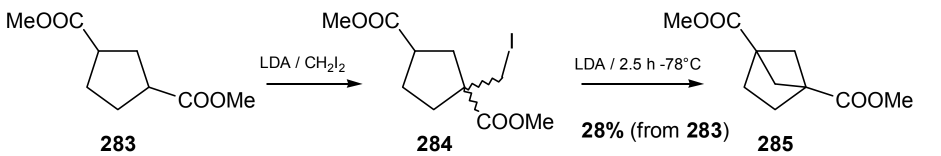
The N-benzyl-2,2,2-trichloro-N-(2-methyl-2-propenyl)acetamide **275** was prepared from N-benzyl-2-methyl-2-propen-1-amine **273** and trichloroacetyl chloride **274** (yield = 80 %). This compound was subsequently ring closed using Cu(I)Cl (1.3 equivalents). After one day of reflux in xylene, no significant reaction had taken place on TLC. Therefore another 1.3 equivalents Cu(I)Cl were added and the mixture was heated under reflux for two more days. The starting material was completely converted and a large new spot could be detected on TLC. After workup and purification the compound was identified as **277** and not the desired pyrrolidinone **276**. Because of the excess of reagent an over reduction took place and the compound was of no further use since the chloromethyl group was gone. No further effort was paid to this reaction because other reaction schemes were more convenient for the preparation of alkyl 4-(chloromethyl)-2-pyrrolidinecarboxylate derivatives.

4.2.2. Using 4-methylene pyrrolidines as starting material

The difficulty in synthesising 4-(halomethyl)-2-pyrrolidinecarboxylates using pyroglutamic acid was the number of functional group transformations needed to reach the end product. Also the reagents to perform these transformations are rather expensive. For this reason other pathways were evaluated potentially leading to 4-(halomethyl)-2-pyrrolidinecarboxylates.



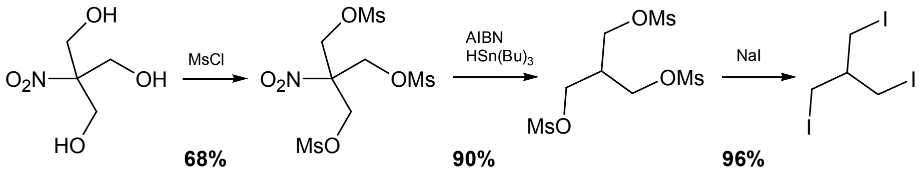
In order to construct a valuable route to the 2-azabicyclo[2.1.1]hexane skeleton, these compounds have to be available in sufficient quantity. The difficulty of this project was foreseen but the C analogue **285**, containing the bicyclo[2.1.1]hexane skeleton, has been prepared through a similar pathway.[117]



The bicyclo[2.1.1]hexane skeleton was synthesised by deprotonation in α-position to the ester function using LDA, and this led to ring closure to the iodomethyl group in β-position (yield = 28%; from **283**).

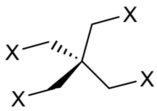
Retro-synthetically the aim was to start from the imine **278** (derived from glycine) and to alkylate it with an appropriate electrophile to **279** and then reduce or hydrolyse the imine **279** to obtain the 4-(halomethyl)pyrrolidine-2-carboxylates **281**. The electrophile of choice was 1,3-diiodo-2-

(iodomethyl)propane **290** which had to be synthesised in 4 steps since it is not commercially available.



286 **287** **289** **290**

The synthesis is easy and uses the cheap commercially available 2-(hydroxymethyl)-2-nitro-1,3-propanediol as starting material.[140] The alkylation of the imine **295** was evaluated with different electrophiles **287**, **289** and **290** but without success (see Table 5). Probably the sterical hindrance of the electrophile is preventing the reaction even though some alkylations using this electrophile are described with good yields in the literature.[141,142] Even more hindered electrophiles with general structure **291** were used in substitution reactions.[143,144,145]



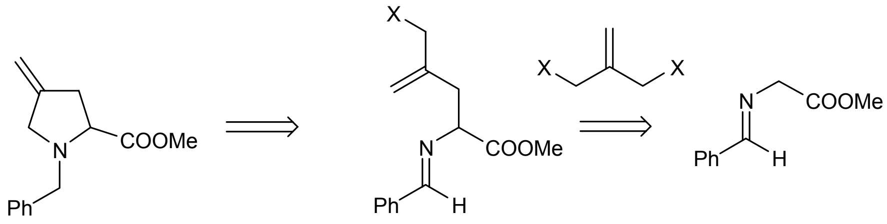
291

Table 5: Evaluated reaction conditions during the alkylation of imine **295**

Electrophile	Reaction conditions	Result
1.2 equiv. **287**	1.5 eqiuv. NaH/ Δ THF on.	No reaction
1.2 equiv. **289**	1.5 equiv. NaH/ DMSO Δ 100°C on.	No reaction
1.1 equiv. **289**	1.1 equiv. LDA/ 0°C, on. to RT	No reaction
1.1 equiv. **290**	1.1 equiv. LDA/ 0°C on. to RT	No reaction
1.1 equiv. **290**	1.1 equiv. NaH/ Δ THF on.	Degradation
1.1 equiv. **290**	1.1 equiv. NaH/ RT THF on.	No reaction

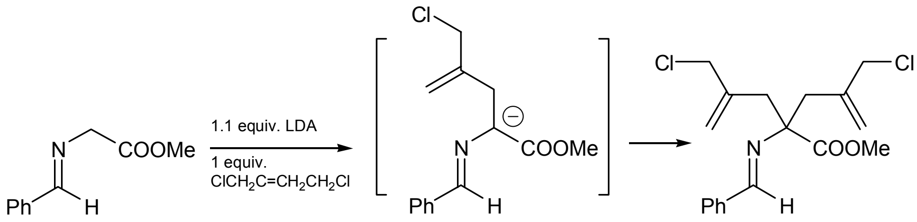
It was clear that a better electrophile should be used which could be converted after its introduction to a useful functionality.

The 3-chloro-2-(chloromethyl)-1-propene[140,146] is a very good electrophile and can lead to a bromomethyl group at the 4-position after ring closure and bromination. After reduction of the imine **294** the desired compound **293** would be formed.



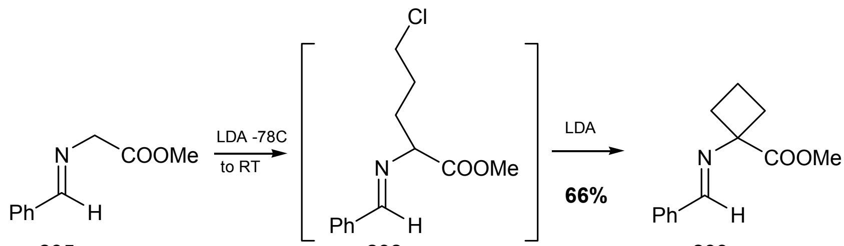
293 **294** **295**

When the alkylation was evaluated using LDA as base (1.1 equivalents) and one equivalent of electrophile, not the mono- but the di-alkylated imine **297** was obtained. This means that the formed anion reacts with the electrophile and that the methine proton of this compound is more acidic than the methylene of the starting material.



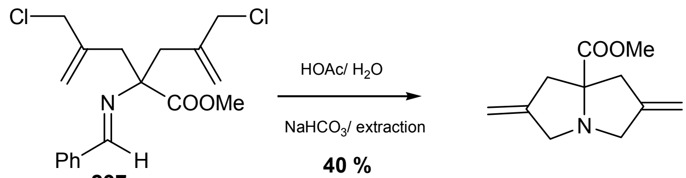
295 **296** **297**

This is different when 1-bromo-3-chloropropane is used as electrophile. In that case, the mono-alkylated derivative **298** can be synthesised and adding an extra equivalent of base led to the formation of a 4-membered ring in good yields (66%).[147]



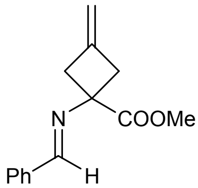
295 **298** **299**

When the dialkylated imine **297** was hydrolysed in acidic medium and the reaction mixture basified before workup, the product cyclised to the methyl 2,6-dimethylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate **300**.



297 **300**

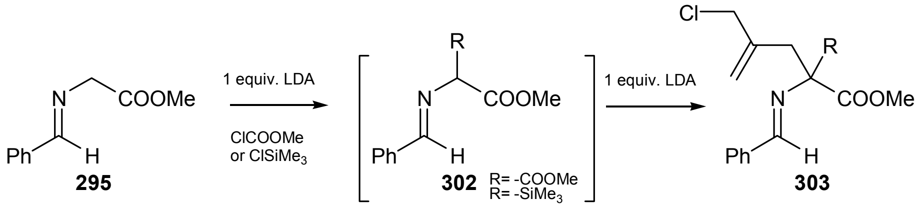
Many biological activities are associated with pyrrolizidines. 8-Substituted pyrrolizidines are useful as muscle relaxants, coronary artery dilators, anti-arrhythmics, anti-hypertensives, blood platelet aggregation inhibitors, anti-histaminics and neuromuscular blocking agents.[148]



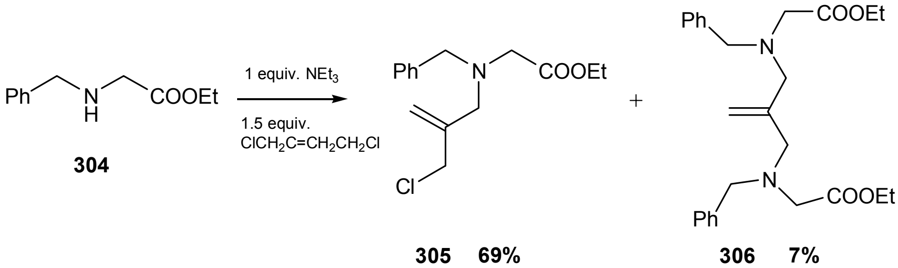
301

In order to further investigate the alkylation on **295** other bases such as KOtBu, BuLi, DBU, LiHMDS (1 equivalent) were evaluated but without success. In all cases (except for DBU where a complex reaction mixture was obtained) the cyclised compound **300** could be obtained after workup. An analogous reaction had already been reported in the literature but in contrast to here, 2 equivalents of base were used in order to form **301** in one step.[149] But even in this case, compound **300** was obtained after workup. Further reactions on this topic were conducted by Nicolai Dieltiens, and the results are discussed in his master thesis.[150]

Because it appeared impossible to mono-alkylate the imine **295** with 3-chloro-2-(chloromethyl)-1-propene, the introduction of a protecting group and subsequent alkylation with 3-chloro-2-(chloromethyl)-1-propene was tested.

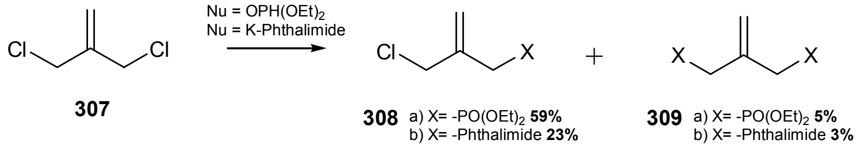


As protecting groups, a methyl carbamate and a trimethylsilyl group were evaluated but in both cases unsuccessfully. To overcome this, a different strategy was developed. Starting from the ethyl (benzylamino)acetate **304**, derived from ethyl glycinate[151,152], the 3-chloro-2-(chloromethyl)-1-propene was first introduced on the N-atom. A mixture of mono **305** and dialkylated product **306** was obtained (69/7).

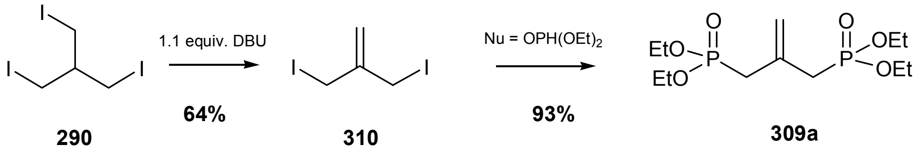


After separation by column chromatography, 69 % of the mono alkylated amino ester **305** was isolated.

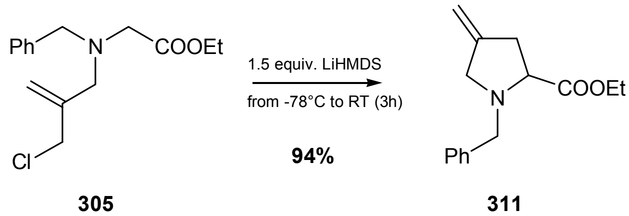
In order to evaluate selective mono-substitution different nucleophiles were initially evaluated. The selective substitution of one of the two chloride atoms was examined using diethyl phosphite[153] and potassium phthalimide as nucleophile.



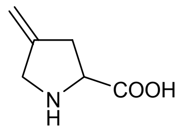
In both cases, mixtures of mono- and di-alkylated products were obtained. Double alkylation could be improved by performing the reaction with **310,** which was prepared by treating **290** with 1.1 equivalents of DBU.[140] Addition of the 3-iodo-2-(iodomethyl)-1-propene **310** to 2 equivalents diethyl phosphite gave compound **309a** in excellent yield (93%).



The ideal reaction conditions to perform the ring closure of **305** were studied. Bases such as LiHMDS, LDA and BuLi were evaluated and gave to a major extent the desired ring closed compound **311**. Allowing the reaction to warm to room temperature led to the formation of some unidentified side compounds and the mixture had to be purified by means of column chromatography. When the reaction was carefully allowed to warm up from -78°C to 0°C over a period of 3 hours followed by quenching at this temperature, no side product was formed and the crude product **311** could be used without any further purification (yield = 94%). The amino ester **311** was prepared through a two step sequence with an overall yield of 65%.

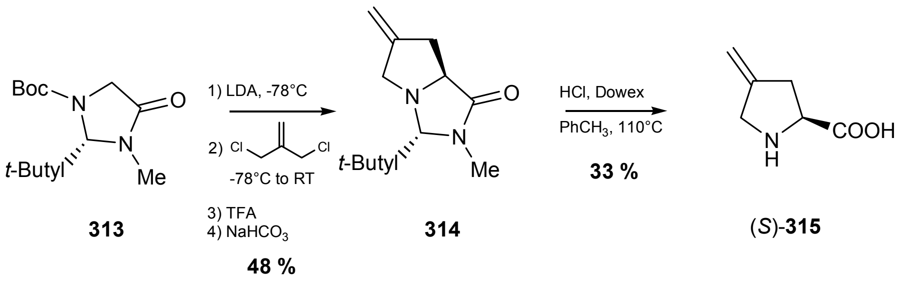


The amino acid **312** has been isolated from loquat seeds (*Eriobotya japonica*)[154,155,156] and, unlike most amino acids, it was present as a racemate. This compound can be synthesised starting from *trans*-4-hydroxy-L-proline,[157,158,159] from pyroglutamic acid[160] or by a radical ring closing mechanism[161] of a suitable propargyl amine. Both methods lead to an enantio pure amino acid. Another very short and interesting pathway used the Seebach's imidazolidinone **313**



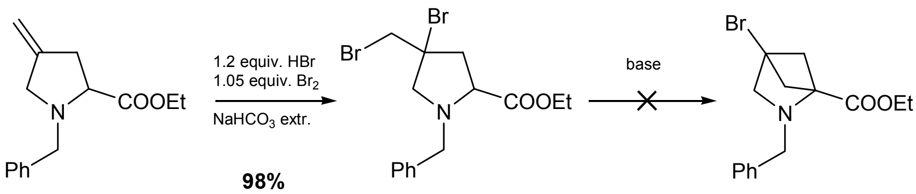
312

(Boc-BMI) to prepare the amino acid **315** in enantio pure form.[162] Although this sequence consists of only 2 steps the overall yield is only 16%.



313 **314** (*S*)-**315**

Bromination of the exocyclic double bond in compound **311** led to the desired 4-bromo-4-(bromomethyl)-2-pyrrolidinecarboxylate **316** (yield = 98%). During the bromination, the N-atom was protected *in situ* as a hydrobromide salt.



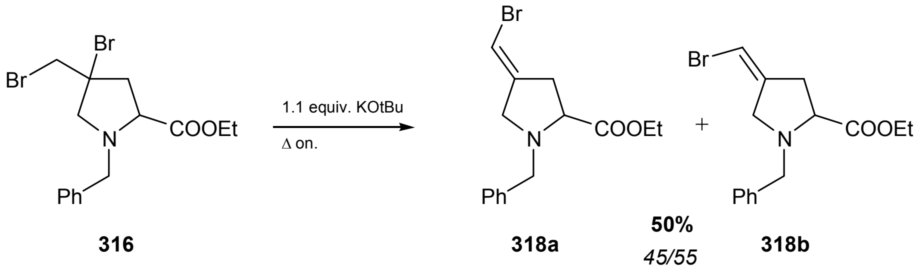
311 **316** **317**

Now that a short and high yielding procedure was available to synthesise 4-bromo-4-(bromomethyl)-2-pyrrolidinecarboxylate **316**, different attempts were undertaken to construct the 2-azabicyclo[2.1.1]hexane skeleton by deprotonation in α-position to the ester group.

Table 6: Evaluated reaction conditions for the ring closure of **316**

Base	Reaction conditions	Result
1.1 equiv. LiHMDS	-78°C to RT/ THF	Mixture of compounds
1.1 equiv. BuLi	-78°C to RT/ THF	Complex reaction mixture
1.1 equiv. LDA	-78°C to RT/ THF	Complex reaction mixture
1.1 equiv. NaH	Δ 1d/ THF	Complex reaction mixture
1.1 equiv. KH	Δ 1d/ THF	Complex reaction mixture

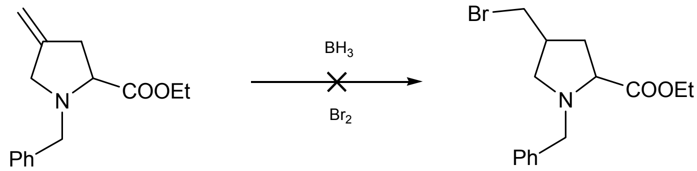
None of the evaluated conditions resulted in ring closure and in some cases elimination of bromide occurred. This elimination appeared to be exocyclic and therefore weaker bases such as DBU or KOtBu were used to prepare the eliminated product in pure form. The use of DBU led to a complex reaction mixture, but adding 1.1 equiv. KOtBu led to the isolation of compounds **318a**,**b** in 50% yield.



316 318a 318b

The fluoro derivatives of compounds **318a**,**b** have already been prepared by performing a Wittig reaction with 4-oxo-L-proline and the ylide of (fluoromethyl)triphenylphosphonium tetrafluoroborate.[157] The E- and the Z-isomer were obtained in a ratio of 4/5. Apparently, in view of the similar spectral data observed, the elimination is indeed exocyclic.

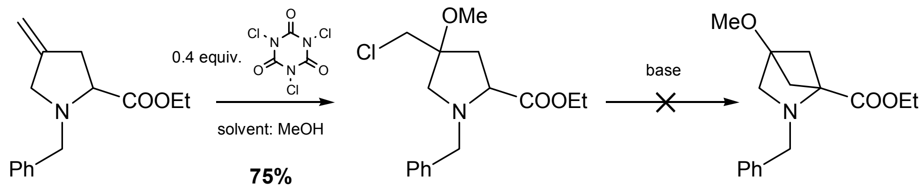
Another method to introduce a bromomethyl group at the 4-position in one step was evaluated. Borane was added to the exo-cyclic double bond and this reaction was worked up with bromine.



311 319

Several of the reaction conditions described in the literature[163,164,165,166] were evaluated but the isolated yield was too low in all cases to make this an interesting pathway.

To avoid elimination, the double bond of **311** was not brominated but treated with methyl hypochlorite. This methyl hypochlorite was *in situ* generated from trichloroisocyanuric acid and methanol.[167] The yield is reasonably good (75%) and led to **320** which should now be protected from elimination because of the introduced methoxy group at the 4-position.

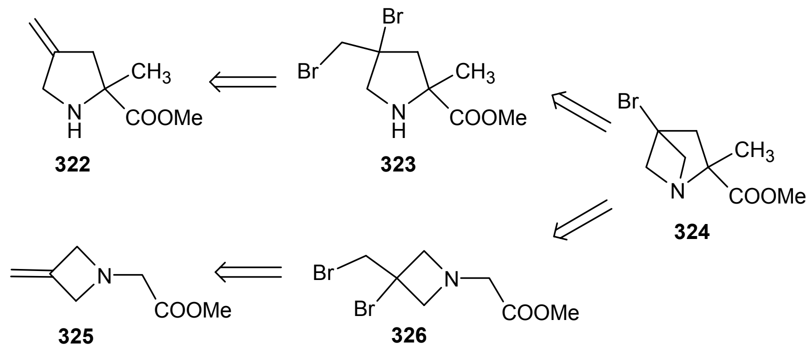


311 320 321

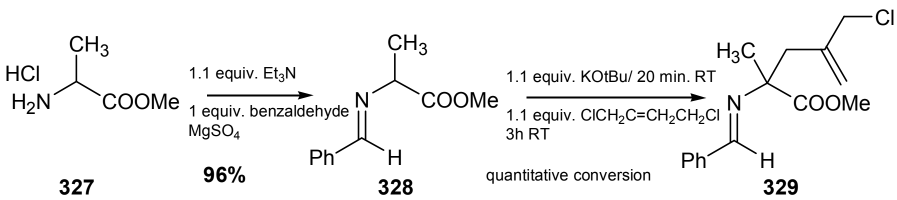
Compound **320** was subjected to treatment with various bases (LiHMDS, LDA, BuLi, NaH, NaH/DMSO) but also here no ring closed product could be isolated. The classical Finkelstein reaction conditions were evaluated to substitute the chloride atom with iodide in the hope that a better leaving group would facilitate the ring closure. Even after refluxing the reaction mixture over 5 days with potassium iodide no reaction took place and the starting material was recovered completely. The synthesis of 2-azabicyclo[2.1.1]hexanes starting from an existing 5-membered ring was finally abandoned because the energy needed to form the desired 4-membered ring seems to be too high.

4.3. Entry to 1-azabicyclo[2.1.1]hexanes

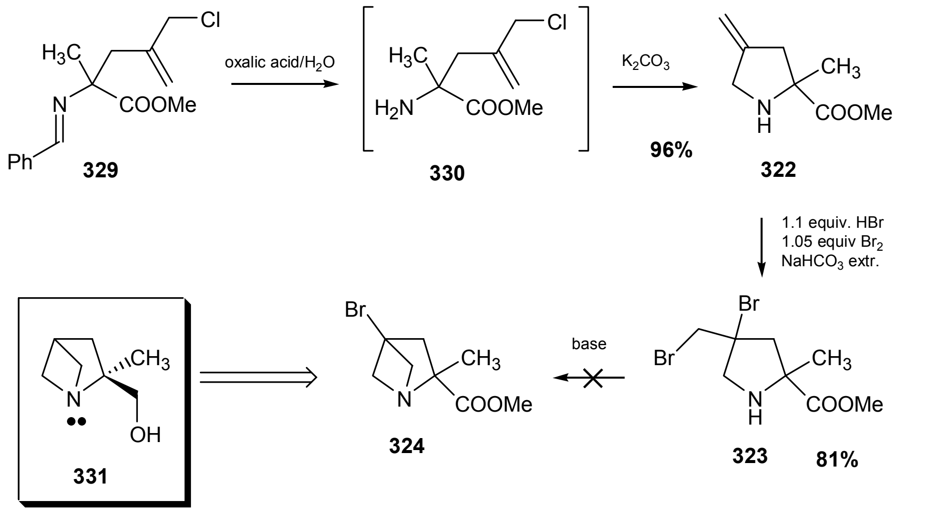
In order to scan some synthetic possibilities of the interesting intermediates, a pathway towards 1-azabicyclo[2.1.1]hexanes was evaluated. Also here, the attempted synthesis of a 4-membered ring in an existing 5-membered ring was planned, but the main difference with the schemes described above is that now the N-atom is supposed to act as the nucleophile.



To avoid possible deprotonation next to the ester group, α-methyl glycine was chosen as starting material. After converting the amino ester to the imine **328**, this compound was alkylated with 3-chloro-2-(chloromethyl)-1-propene using KOtBu as base (yield = 74%).

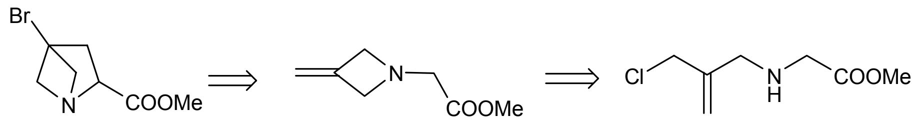


To evaluate the ring closure, a free amine is needed and therefore the imine **329** was hydrolysed using a saturated aqueous oxalic acid solution.



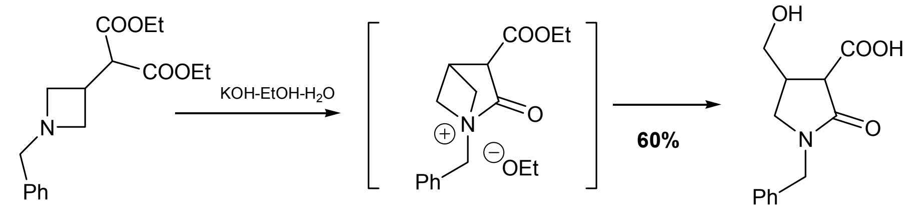
The reaction mixture was subsequently extracted to remove the formed benzaldehyde. The water phase was basified using a saturated K_2CO_3 solution and the aqueous mixture stirred at room temperature. After 20 minutes the compound was converted to the desired methyl 2-methyl-4-methylenepyrrolidine-2-carboxylate **322** in very good yield (96%). This product was brominated using the classical procedure and compound **323** was obtained. The ring closure was evaluated with and without base. In most cases, a complex reaction mixture was obtained, however in other cases the starting material was recovered totally. The goal was to evaluate this strategy and to obtain a very constrained bicyclic structure which could be transformed to a chiral auxiliary **331** (when an enantioselective alkylation was performed).

Another pathway leading to the same type of compounds was evaluated.



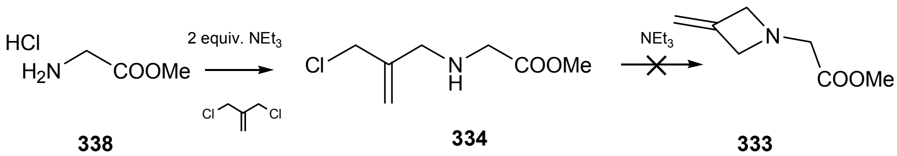
332 **333** **334**

A more successful synthesis might be achieved by first synthesising the 4-membered ring and preparing the 5-membered ring afterwards. An analogous kind of ring closure has been proposed to proceed through the unstable ammonium intermediate **336**.[168]



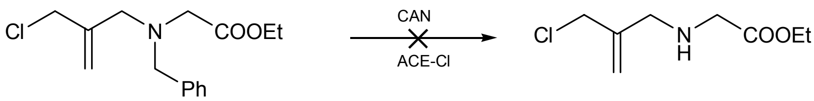
335 **336** **337**

In our case, the end product **332** would probably be stable. Therefore, methyl glycinate was alkylated on nitrogen using 3-chloro-2-(chloromethyl)-1-propene. The main problem was the instability of the formed product **334**. Methyl {[2-(chloromethyl)-2-propenyl]amino}acetate was prepared and isolated but the product polymerised rather rapidly. This is obvious since there is a free amine and an allylic chloride present in the same molecule. Evaporation and thus concentration accelerates the polymerisation process.



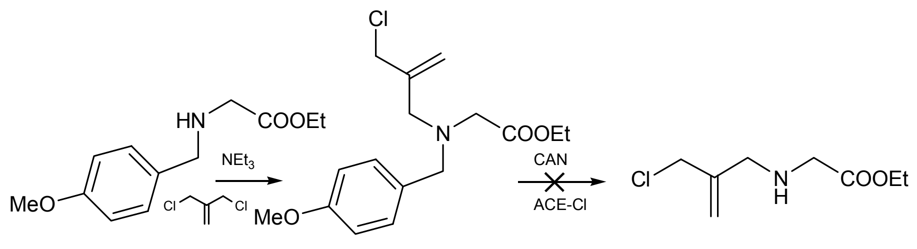
338 **334** **333**

The ring closure of **334** was evaluated without base in diluted conditions (2% solution in THF). Stirring the mixture at room temperature overnight did not affect the starting material, but after refluxing the reaction for 1 day in THF the molecule broke down. Since the structure of **334** was only confirmed by H, C and IR spectra and no mass spectrum was obtained, attempts to remove the benzyl group of **305** were undertaken to prove the structure.[169,170,171]



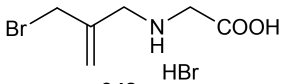
305 **339**

Despite all efforts using CAN or ACE-Cl, the deprotected amino ester **339** could not be isolated. A classical way to remove a benzyl group is hydrogenation, but in this case it would not only deprotect the N-atom but also hydrogenate the double bond and probably remove the chloride atom. To facilitate the removal of the benzyl group, a derivative carrying a p-methoxybenzyl group was prepared.[172,173]



340 **341** **339**

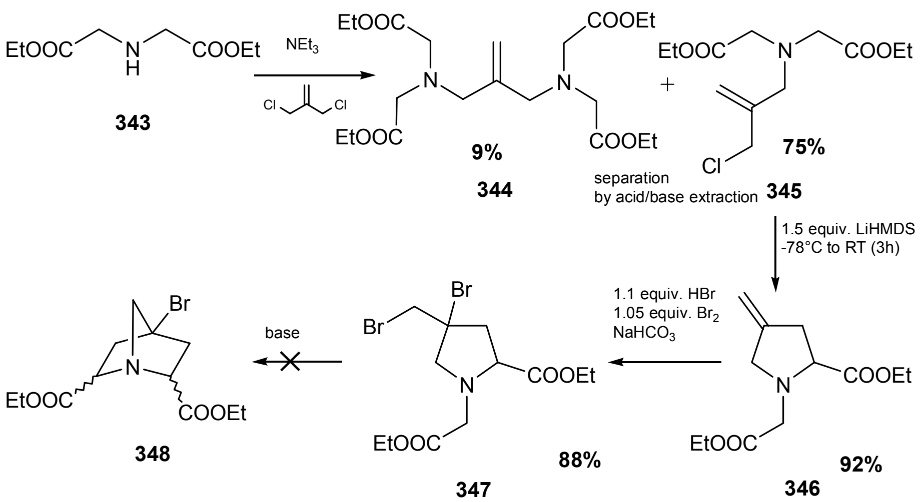
Again deprotection of **341** using CAN or ACE-Cl gave bad results. In a last attempt to remove the N-protecting group hydrobromic acid was used. By refluxing compound **341** in a concentrated hydrobromic acid solution the free amino acid **342** was obtained. The main problem was that it could not be used further, since deprotection of the N-atom immediately resulted in degradation of the starting material.



342

4.4. Entry to the 1-azabicyclo[2.2.1]heptane skeleton

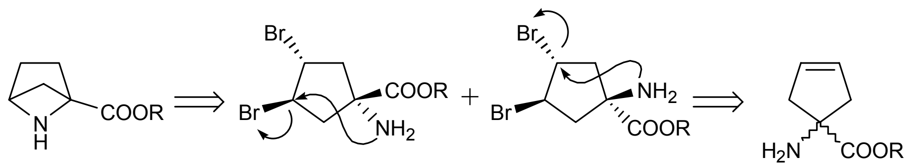
Much research has been conducted concerning the biological activity of bicyclic glutamic acid analogues. A possible pathway to the 1-azabicyclo[2.2.1]heptane-2,6-dicarboxylate skeleton was evaluated starting from **343**.



The N-atom was alkylated using 3-chloro-2-(chloromethyl)-1-propene (1.5 equivalents) as electrophile. After refluxing the reaction mixture overnight, a mixture of mono-substituted and diamino product was obtained. In the previous case where ethyl (benzylamino)acetate **304** was alkylated with 3-chloro-2-(chloromethyl)-1-propene, the two compounds had to be purified by column chromatography. In this specific case a simple acid/base extraction was sufficient to separate the compounds. Due to its decreased basic character the mono-amine product (bearing two ester groups in α-position) remained in the organic phase when performing the extraction with a 2N HCl solution, while the the diamine was extracted in the water phase. After making alkaline, the water layer and extraction with dichloromethane, most of the dimer **344** and some traces of **345** were found. Compound **345** can easily be ring closed to **346** using 1.5 equivalents of LiHMDS. The period of 3 hours to allow the reaction to warm up 0°C should be carefully monitored since allowing the reaction to warm to room temperature led to the formation of side products. It is worthwhile to note that compound **346** can be synthesised on large scale and can be purified through a acid/base extraction. This however is only true if the extraction is performed with equal amounts of solvent as described in the experimental part. Bromination of the exo-cyclic double bond gave compound **347** in good yield. Different bases (LDA, LiHMDS) and reaction conditions were evaluated to synthesise the bicyclic glutamic acid analogue **348** but no conditions leading to the desired end product could be found. In all cases a complex reaction mixture was obtained.

4.5. Attempted synthesis of the 5-azabicyclo[2.1.1]hexane-1-carboxylate skeleton

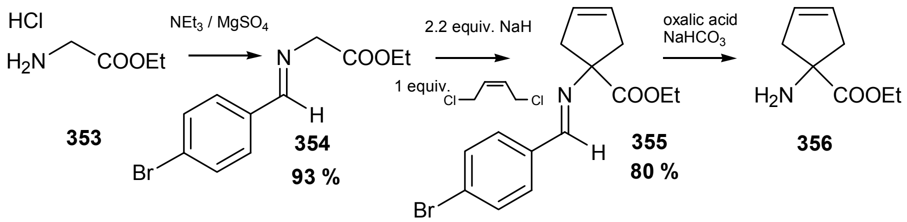
In the scheme above, attempts were undertaken to construct the 2-azabicyclo[2.1.1]hexane skeleton by ring closure of a suitable chloromethyl group in an existing 5-membered ring. It appeared impossible for the generated anion to reach the chloromethyl group and to form the bicyclic skeleton. The anion is part of the 5-membered ring and therefore less flexible. The ring closure was now evaluated using an amino-group as substituent on the 5-membered ring.



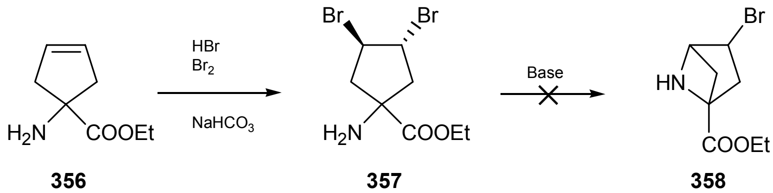
349 **350** **351** **352**

The main difficulty of this procedure is for sure the extra ring strain and the substitution on a secondary carbon atom. However, this might not be such a problem since intramolecular substitutions often proceed better when the nucleophile and the electrophile are properly oriented.[174] Bromination of the amino ester would lead to compounds **350** and **351**. In both cases the amino group can substitute, theoretically, one of the two bromine atoms.

The amino ester **350** could be prepared starting from imine **354** which can be obtained in a straightforward manner from ethyl glycinate. This compound **354** could be alkylated using sodium hydride as base and (2Z)-1,4-dichloro-2-butene as electrophile followed by hydrolysis with oxalic acid.[175,176,177]



This compound could be prepared on multi-gram scale. During bromination, the amino group was protected as a hydrobromide salt to avoid side reactions. Once this compound **357** was obtained several conditions were evaluated to make the 1-ethoxycarbonyl-5-azabicyclo[2.1.1]hexane skeleton. In none of the evaluated conditions the ring closed product **358** could be detected. When using no base or a weak base the starting material was totally recovered and no reaction took place.

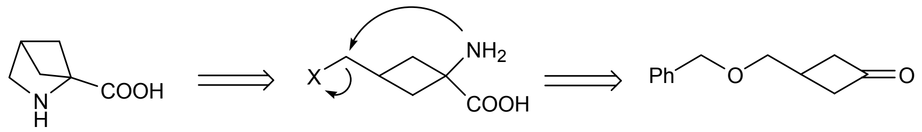


On the other hand, when strong bases were used, lithium halogen exchange and elimination occurred. It was clear that all the pathways starting from a 5-membered ring would not lead to the desired bicyclic skeleton. Therefore this route was abandoned and new pathways were developed to synthesise the 2-azabicylclo[2.1.1]hexane skeleton.

4.6. Entry to the 2-azabicyclo[2.1.1]hexane skeleton using cyclobutanone derivatives

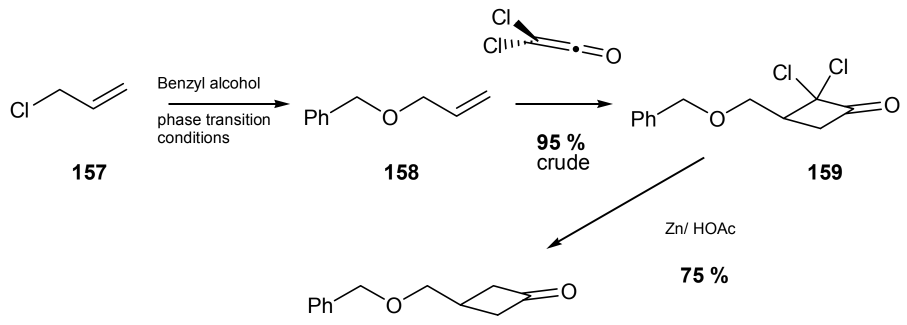
4.6.1. Synthesis of the natural 2,4-methanoproline

Retro-synthetically the natural amino acid 2,4-methanoproline **3** can be synthesised from a suitable cyclobutanone by transformation of the keto-function to an amino acid.



3 359 160

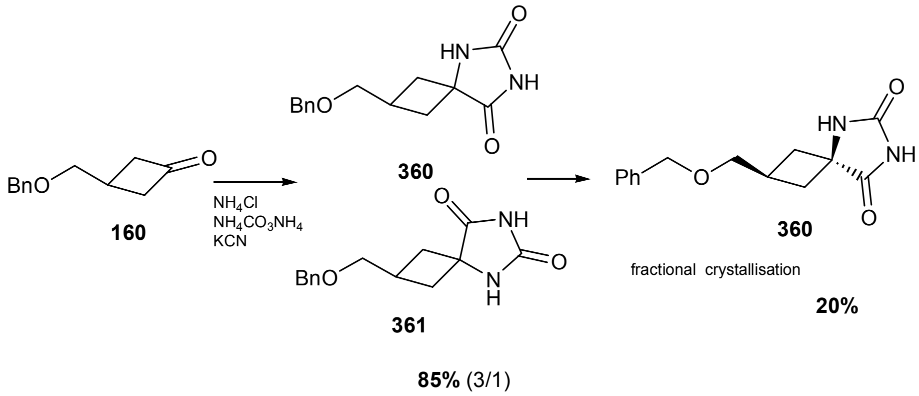
The cyclobutanone **160** was chosen as starting material. Allyl benzyl ether appeared to be a good candidate to perform the [2+2]-cycloaddition reaction because the ether function can probably be converted to a good leaving group. This cycloaddition was already described in literature[83,84] but the same conditions were used as these for the preparation of the 3-(chloromethyl)cyclobutanone since these gave better results (see page 64). After optimizing the reaction conditions, the desired cyclobutanone **159** could be prepared with a crude yield of 95%. Higher total yields of the dehalogenated product **160** were obtained when the crude product was first dehalogenated prior to distillation.



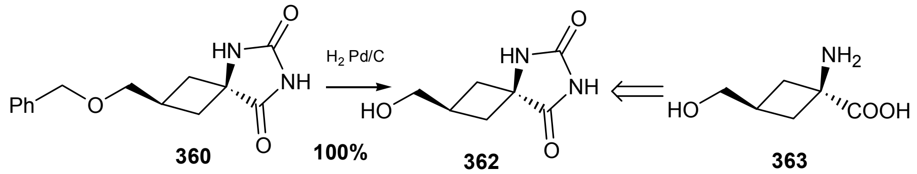
160

The synthesis could be performed on a large scale and more than 70 gram of this compound was prepared. The dehalogenation of the geminal chloride atoms proceeds in 75% yield (after distillation).

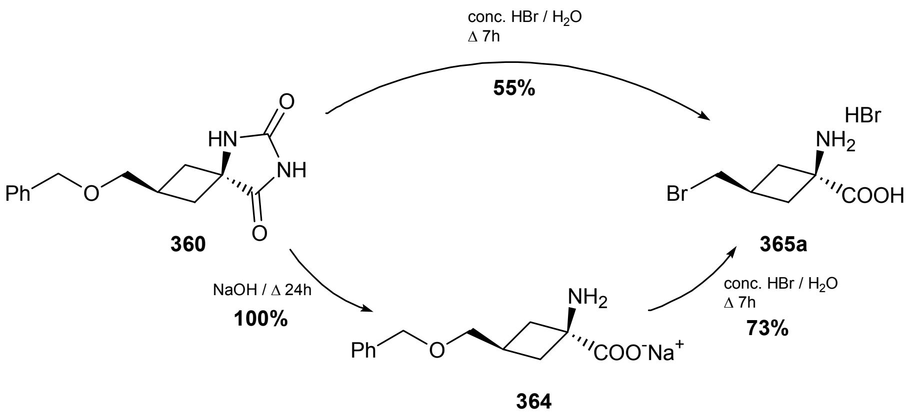
The idea was to synthesise the amino acid group first and to convert the ether group to a suitable leaving group afterwards. To synthesise the amino acid, the Bucherer-Bergs synthesis was used since in most cases the obtained hydantoines are crystalline. The hydantoin **360**, **361** could be prepared using ammonium chloride, ammonium carbonate and potassium cyanide in a mixture of methanol and water (1/1) as solvent. The crystalline compound was obtained in good yield (85%) as a mixture of two *cis*-*trans* stereoisomers (3/1). The major component turned out to be the desired ($BnOCH_2$, NH_2)-*cis*-isomer as shown by subsequent cyclisation (see below).



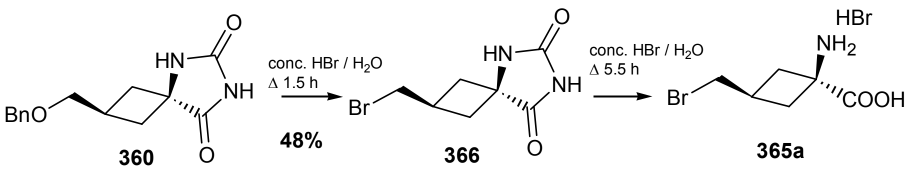
This means that 25% of the compound (*trans*-isomer) cannot lead to the desired amino acid. The observed selectivity can be attributed to the steric interaction of the 3-benzyloxymethyl substituent on the cyclobutanone ring during the formation of the hydantoin, *i.e.* during the addition of cyanide onto the imino species. Since only the *cis*-isomer can lead to ring closure a separation of the diastereoisomers was performed. This separation proved to be difficult and only fractional crystallisation was successful. Although the yield dropped significantly (20%), the *cis*-isomer could be prepared in high purity. Hydrogenation of the benzyl ether gave, almost quantitatively, the alcohol. The idea to convert this alcohol to a suitable halogen in one step and to synthesise the amino acid in a second step was not performed because this would make the pathway too long.



Alternatively, the deprotection of the ether function, the conversion of the resulting primary alcohol to the corresponding alkyl halogenide and the liberation of the amino acid were performed in a one-pot reaction. To achieve this, the hydantoin **360** was refluxed for 7 hours in a concentrated hydrobromic acid solution (48% HBr in water). Because of the harsh reaction conditions during these conversions, some unidentified side products were formed. Nevertheless the amino acid **365a** could be isolated in moderate yield (55%). These side reactions could be circumvented by performing the reaction in two steps. Firstly the hydantoin was hydrolysed with a sodium hydroxide solution (0.5N, Δ 24h) and the amino acid **364** was obtained quantitatively. The ether functionality was subsequently converted to the 3-(bromomethyl)cyclobutane amino acid **365a** by heating in a concentrated HBr acid solution during 7 hours. The overall yield was better (73%) and no side products were formed.

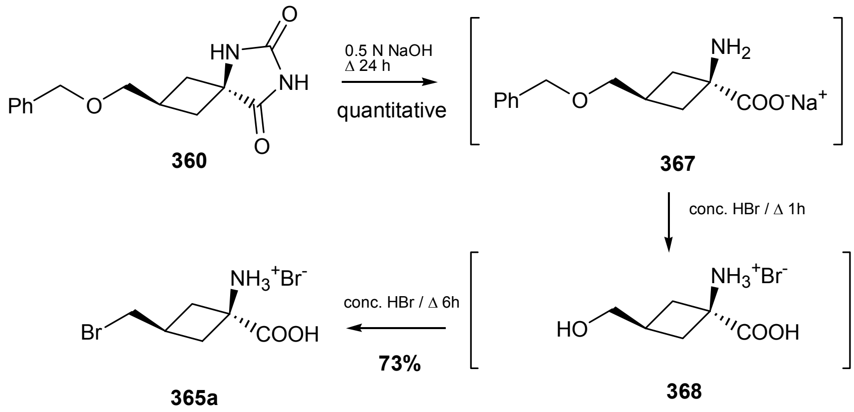


Because several reactions were done in one step, the reaction was stopped from time to time to analyse the reaction pathway and to identify the intermediates. In the first sequence the hydantoin **360** was converted in one step to the desired amino acid **365a**. When the reaction was stopped after 1.5 hours of reflux, the interesting intermediate hydantoin **366** could be isolated by extraction with diethyl ether. After vigorously shaking the two layers many white crystals appeared between the organic and the water layer. These crystals dissolved better in the water phase than in the organic phase so an extra amount of water was added until all the crystals were dissolved. Evaporation of the water phase led to the isolation of the hydantoin **366** with a yield of 48%.

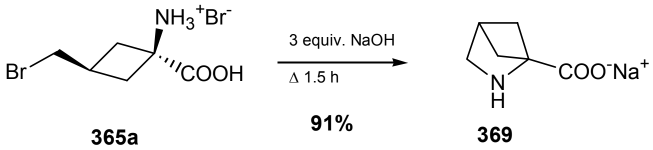


This very interesting intermediate illustrates that the conversion of the ether function to the bromomethyl group proceeds quite rapidly but the hydrolysis of the hydantoin is a slow reaction. To hydrolyse the hydantoin an additional refluxing period of 5.5 hours is needed.

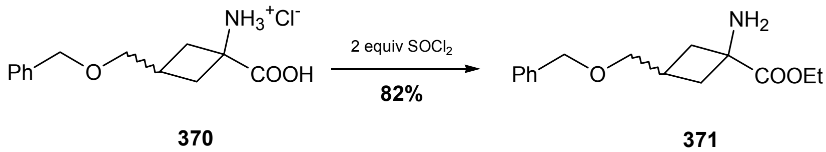
However, when the hydantoin was first hydrolysed to the corresponding amino acid and this compound **367** was heated for 1 hour in a concentrated hydrobromic acid solution the ether was almost completely deprotected with the formation of the alcohol **368** and benzyl bromide. Further refluxing led then eventually to the same amino acid **365a**.



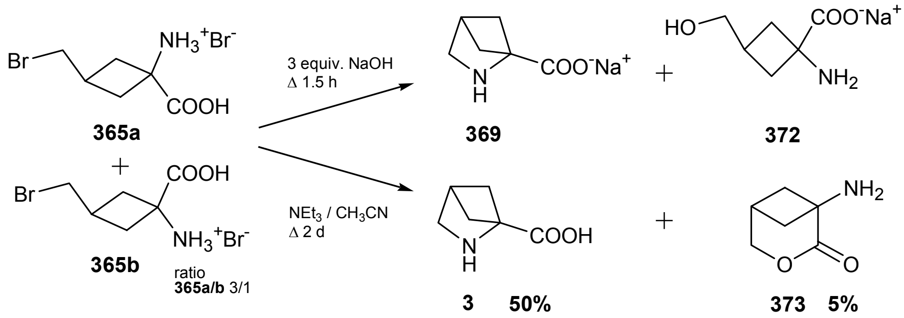
In order to build the 2-azabicyclo[2.1.1]hexane skeleton, the amino acid **365a** was refluxed in a sodium hydroxide solution and was quantitatively converted to 2,4-methanoproline (Na-salt). After crystallisation the amino acid was obtained in 91% yield.



Using this sequence 2,4-methanoproline was synthesised in 7 steps with an overall yield of 9% (see overview 1; page 63). The advantage of this procedure lays in the possibility to perform it on a quite large scale, whereas this can be problematic with the currently available procedures. The main disadvantage is the low yield in the fractional recrystallisation of the hydantoin **360**. Some attempts to perform the separation of the isomers on the amino ester **371**, prepared using thionyl chloride, were also unsuccessful.

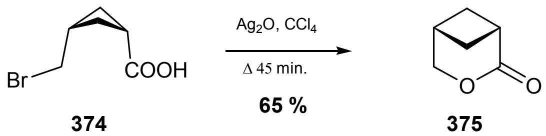


Alternatively, the separation was done in the last step instead of on the level of the hydantoines **360**, **361**. The main problem was that the separation of the two amino acids **369** and **372** was very difficult. To avoid difficult separations reaction conditions were studied to transform the two isomers in a way that one isomer becomes soluble in water while the other dissolves in an organic solvent.

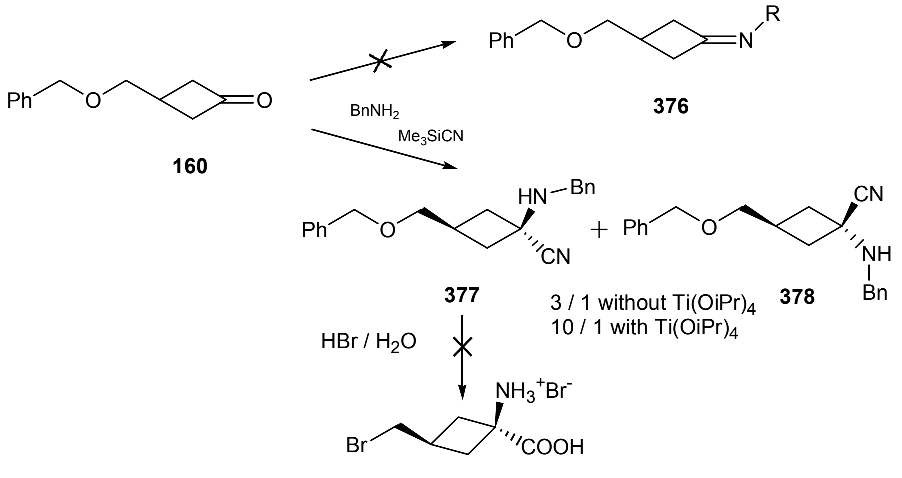


For the ring closure, the solvent should be moisture free and still be sufficiently polar to dissolve the starting material **365a**,**b**. Preparing the free amine using triethyl amine and refluxing this mixture in acetonitrile for 2 days gave a mixture of two compounds. All the solvent was removed and the product, a white powder, was washed thoroughly with dry diethyl ether. The filtrate only contained the organic soluble compound. After evaporation of the solvent, the bicyclic lactone **373** was isolated as a pure compound. Although the yield was low (5%), it should be noted that the maximum yield of this compound is 25%, *i.e.* one quarter of the *trans*-isomer was present in the starting material. The white powder contained the 2,4-methanoproline in almost pure form, and after recrystallisation, the amino acid could be obtained in 50% yield (maximum yield 75%). This is a very useful improvement to separate the two isomers since this procedure can be performed on large scale.

The lactonisation reaction of **365b** was inspired by the work of Musso.[178] Lactone **375** was prepared from the corresponding *cis*-3-(bromomethyl)cyclobutanecarboxilic acid **374** in 65 % yield using silver oxide in refluxing CCl_4.

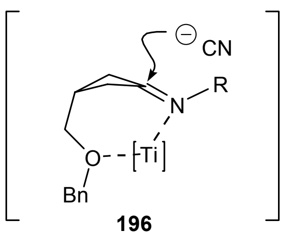


The yield of this pathway depends on the ratio of isomers of compound **360** and **361**. Improving this ratio would lead to a higher yield of isolated 2,4-methanoproline. Therefore, another method was evaluated to convert the keto-function of the cyclobutanone **160** to the corresponding amino acid.



365a

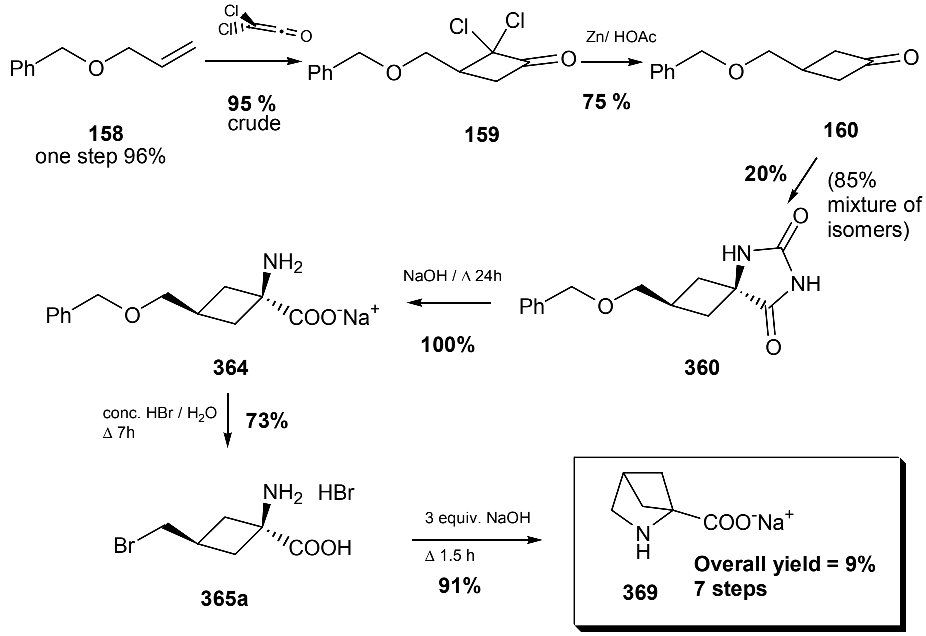
The idea was to synthesise the imine **376** first and to add hydrogen cyanide onto this functional group to prepare the amino nitrile. Unfortunately it was impossible to prepare the imine using Ti(IV)Cl. Probably the titanium complexed with the oxygen present in this molecule leading to unwanted side products. However, the complexation of the titanium could be used in the direct preparation of the amino nitrile and thus improve the selectivity. To evaluate this, benzyl amine and trimethyl silyl cyanide were added to the cyclobutanone and the amino nitrile could be isolated in very good yields (98%) as a mixture of two isomers (3/1 *cis/trans*). In another reaction, the cyclobutanone **160** was reacted with benzyl amine and titanium tetra-isopropoxide. After 2 hours the trimethylsilyl cyanide was added. If there exists a complex **379** between the titanium and the oxygen, then the selectivity of the reaction should be improved. Indeed, the ratio changed from 3/1 to 10/1. This means only 10 % of unwanted isomer instead of 30%. Attempts were made to convert the amino nitrile **377** in one step to the amino acid **365a** using hydrobromic acid, but in all analysed reaction conditions too many side products were formed so this was no effective improvement.



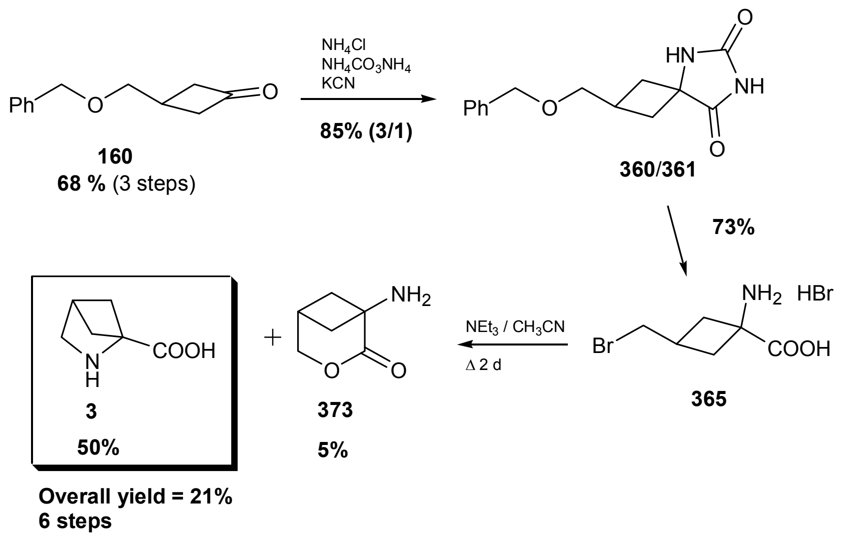
196

OVERVIEW 1

Using these sequences, 2,4-methanoproline could be synthesised through 2 pathways. In the first the separation of isomers was performed by a fractional crystallization on the hydantoin **360**.

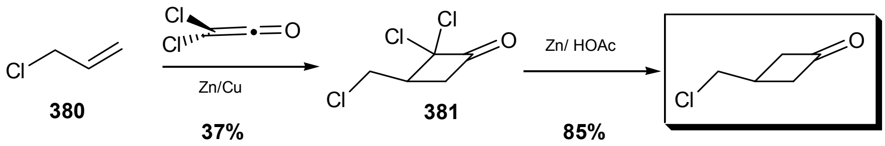


In the second procedure the separation was performed in the last step. The overall yield is now improved up to 21% in 6 synthetic steps.



4.6.2. Synthesis of 3-halomethylcyclobutanones

As described in the literature part, only one synthesis of 3-(chloromethyl)cyclobutanone is known. Unfortunately, the pathway is very long (9 synthetic steps) and the overall yield of 3-(chloromethyl)cyclobutanone was only 6%.[37] It is needless to say that the pathway to synthesise 2-azabicyclo[2.1.1]hexanes would only be valuable when a new and shorter synthesis of 3-(chloromethyl)cyclobutanone is found. A major objective of this dissertation was to find new entries to 3-halomethylcyclobutanones. Two main pathways were evaluated. The first and most straightforward, but probably the most difficult, is the [2+2]-cycloaddition of dichloroketene and allyl chloride. The initial experiments gave the desired product **381** only in very low yields (< 5%). Even though the yield was low, a search was started to improve this yield because it would probably be the shortest pathway (2 steps) to prepare 3-(chloromethyl)cyclobutanone **37**.

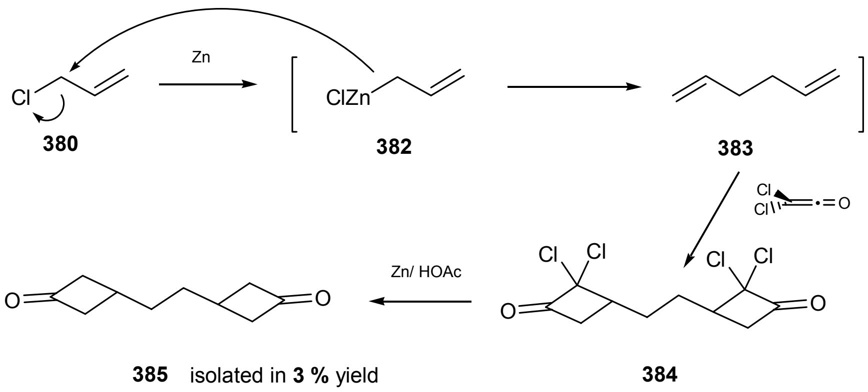


380 **381** **37**

overall yield = **31%**
2 steps

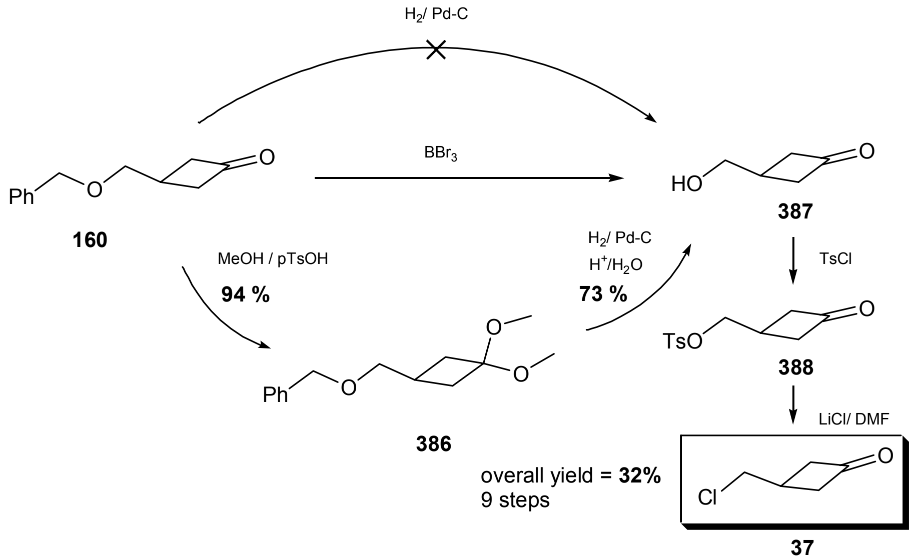
After repeating the reaction under more than 20 different reaction conditions, the yield was improved up to 37%. This is quite low but a major breakthrough. The dichloroketene was generated *in situ* from trichloroacetyl chloride and a Zn/Cu couple. The preparation of this Zn/Cu couple is of crucial importance: insufficient drying of this reagent leads to low yields of isolated product (2 hours at room temperature under a vacuum of 0.2 mmHg). The reaction mixture consists mostly of **381**, together with some small amounts of side products and the reaction is extremely regioselective. Attempts to generate dichloroketene from dichloroacetyl chloride and a base gave complex reaction mixtures in all cases. The bases triethylamine and 2,6-lutidine were evaluated but unsuccessfully. The cycloaddition was also evaluated using allyl bromide but in this case organo-zinc compounds were formed instead of the cyclobutanone.

Compound **381** is a direct precursor of the 3-(chloromethyl)cyclobutanone **37**. The 2 geminal chlorine atoms can be removed with zinc in acetic acid through a free radical reduction process. With this new procedure, 3-(chloromethyl)cyclobutanone **37** can be synthesised in 2 steps with an overall yield of 31**%**. After the removal of the geminal chloride atoms and distillation of the end product **37**, some residue was formed and remained in the flask as an oil. Residues constitute a loss of compound and therefore it was analysed thoroughly. Apparently it consisted of one major compound namely the dimer **385**. At first it was not really clear in which step the dimer was formed since compound **381** was not purified prior to distillation of **37**. To exclude the possibility of dimerisation during distillation the pure 3-(chloromethyl)cyclobutanone **37** was heated with 0.5 equivalents of zinc without solvent at 100°C. After this heating period of 3 hours all the starting material was recovered and no dimerised product was formed.



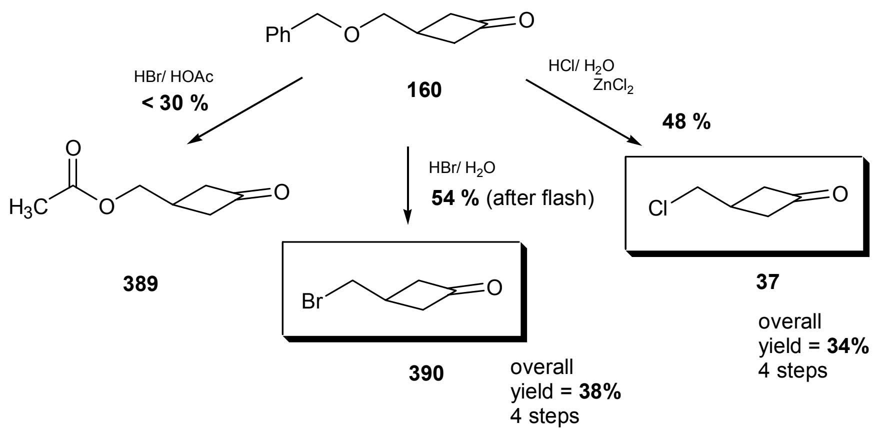
A more logical answer is that dimerisation occurred in the first step. This means before the cycloaddition took place. At that time, a lot of allyl chloride is present and some of it reacts with zinc to give an organo-zinc compound. This organic-metallic compound **382** reacts again with allyl chloride to give 1,5-hexadiene **383**. The cycloaddition takes then place on allyl chloride as well as on **383**.

Because the cycloaddition of allyl chloride and dichloroketene had a low yield, a search was conducted to find an alternative alkene. The cyclobutanone **160**, as described in the previous part would be a good precursor for the 3-(chloromethyl)cyclobutanone.



The initial idea was to deprotect the benzyl ether[179] by catalytic hydrogenation leading to the alcohol **387**. The conversion of this alcohol to a chloride had already been described (see literature part; page 18).[37] Unfortunately, hydrogenation proved not to proceed selectively, probably because partial reduction of the carbonyl group took place.

Deprotection of the benzyl ether could however be performed using BBr_3 or BCl_3.[180] Three equivalents of BBr_3 were added to the ether **160** at 0°C in dichloromethane. After workup with a small amount of water, the 3-(hydroxymethyl)cyclobutanone **387** was present in the organic phase. Because this was only a small fraction, the water phase was evaporated and almost pure 3-(hydroxymethyl)cyclobutanone **387** could be isolated indicating its high solubility in water. This reaction illustrates that it is possible to prepare the 3-(hydroxymethyl)cyclobutanone in this way. The important disadvantages were the solubility of the end product and the expensive boron tribromide, especially if the reaction would be performed on a large scale. To overcome this, the carbonyl group was first converted to an acetal since this group is resistant to hydrogenation conditions. Indeed, deprotection of the acetal **386** occurred and after hydrolysis the 3-hydroxymethylcyclobutanone **387** was isolated in 73% yield. This alcohol can be converted using the known procedure in 4 steps to the 3-(chloromethyl)cyclobutanone **37**. The overall yield is almost the same as in the previously described procedure but instead of 2 steps, 9 synthetic reactions are necessary. Especially the functional group transformation to convert the ether to a chloride lengthened the pathway.

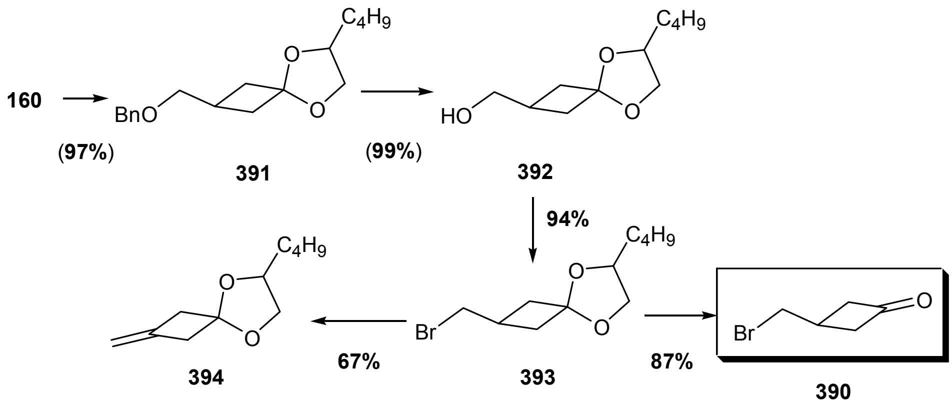


The deprotection of the ether and conversion to the alcohol could be performed in the same step by refluxing the product in a concentrated hydrochloric acid solution using zinc dichloride as Lewis-acid. In this way, the reaction sequence was shortened to 4 reaction steps with an overall yield of 34%.

Performing the reaction with a concentrated hydrobromic acid solution in acetic acid, a mixture was obtained but the major compound could be identified as **389**.

Using a concentrated solution of hydrobromic acid in water (48% HBr in H_2O) led to the formation of 3-bromomethyl cyclobutanone **390**, which after purification by column chromatography, was isolated with a yield of **54%**.

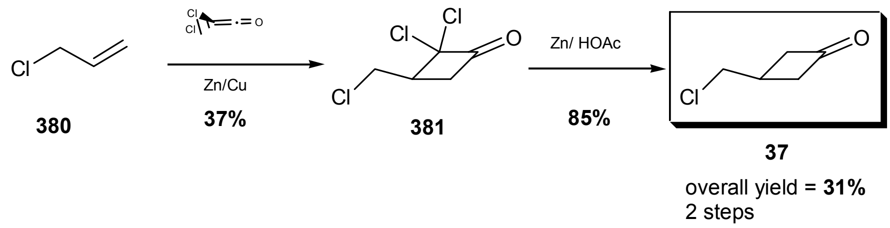
Very recently (2003), a different laboratory referred to one of our articles[181] describing an analogous pathway to prepare 3-(hydroxymethyl)cyclobutanone **387** and 3-bromomethylcyclobutanone **390** starting from the same cyclobutanone **160**.[182]



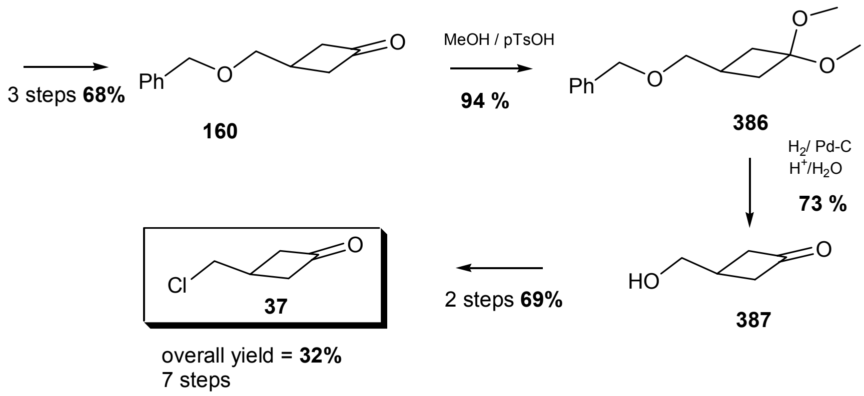
They re-evaluated the direct hydrogenation of this cyclobutanone **160** and also concluded as we did that it was impossible to perform the reaction selectively. Instead of the dimethoxy acetal **386** they prepared the acetal using ethylene glycol or 1,2-hexanediol. Only the acetal **391** gave satisfactory results and compound **392** was isolated in 99% yield. The alcohol group was further converted to the bromo derivative **393** in excellent yields (94%). After hydrolysing the acetal function the 3-bromomethylcyclobutanone **390** was obtained (yield 87%). Although the yield to convert the cyclobutanone **160** to 3-bromomethyl cyclobutanone was improved (78% from **160**), 4 functional group transformation steps were necessary to prepare this compound. In our procedure all conversions were performed in one single step with moderate yield (54%) and using only hydrobromic acid as very cheap reagent. Which procedure is more preferable, depends on the further reactions planned.

OVERVIEW 2.

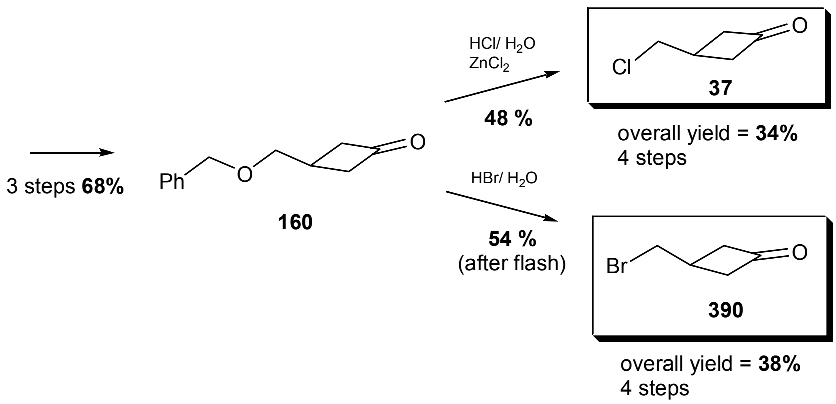
Some different procedures were developed to prepare the 3-(chloromethyl)cyclobutanone **37**. In the first and most straightforward method, allyl chloride is reacted with dichloroketene. Removing the geminal halogens resulted in the 3-(chloromethyl)cyclobutanone (2 steps; overall yield 31%).



In a second pathway the cyclobutanone **160** was converted to the end product using different synthetic steps and shortcuts.



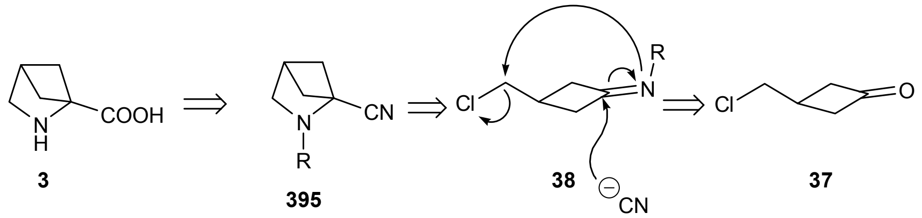
This pathway could be shortened by deprotecting the ether of **160** and converting the alcohol in the same step. In this way the reaction sequence was shortened to 4 steps (overall yield of 34%).



4.6.3. Synthesis of the 2-azabicyclo[2.1.1]hexane skeleton

4.6.3.1. Retro-synthetical approach

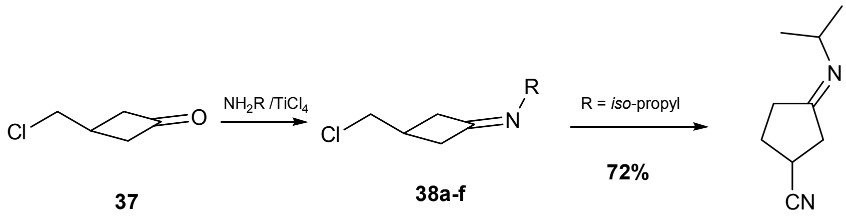
Retro-synthetically the idea was to convert the 3-(chloromethyl)cyclobutanone **37** to the corresponding imine **38** which could undergo an intramolecular nucleophilic ring closure using cyanide as nucleophile. After removal of the N-protecting group, hydrolysis of the nitrile would lead to the natural 2,4-methanoproline.



3 395 38 37

4.6.3.2. Synthesis of imines and amino nitrils derived from 3-chlorocyclobutanone

No problems were to be expected during the preparation of the imines since some derivatives were already described in the literature.[37] The imines were obtained in good yield and the compounds were subjected to a cyanide addition to evaluate the ring closure.[183,184,185]

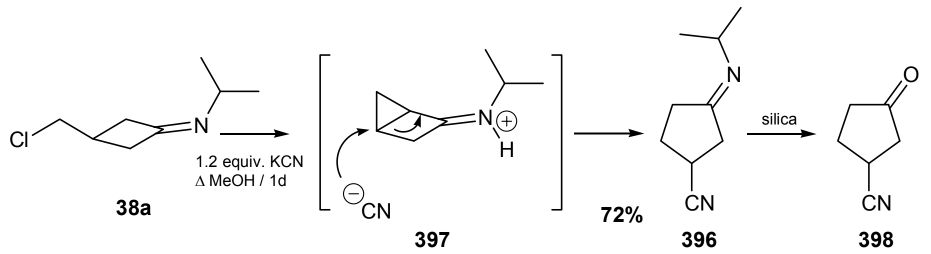


37 38a-f 396

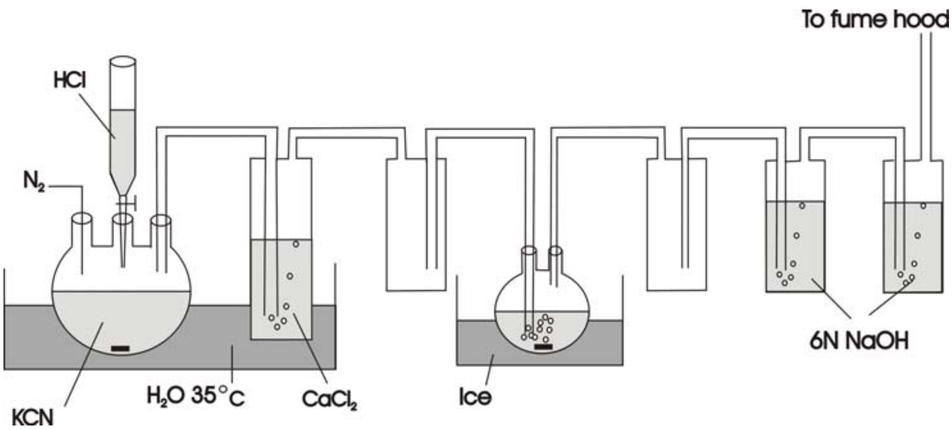
Table 7: Yield of the synthesised imines **38a,b,c,d,e,f**

R=	Yield
a) -iso-propyl	80 %
b) -t-butyl	76 %
c) -iso-butyl	77 %
d) -allyl	89 %
e) -n-propyl	95 %
f) -benzyl	89 %

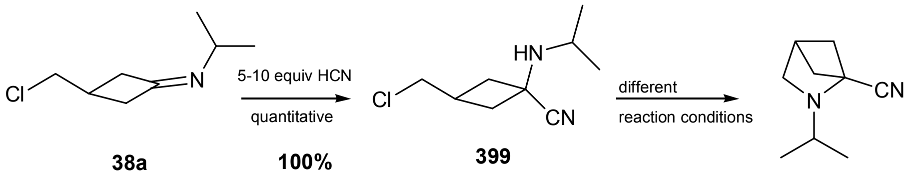
When the isopropyl imine **38a** was treated with cyanide, not the bicyclic compound **395** was obtained but the cyclopentane derivative **396** was isolated in 72% yield. The imine **38a** proved to be rather unstable in basic conditions and a side reaction took place. This reaction proceeds probably through the bicyclic intermediate **397**, which is very constrained and undergoes a ring expansion by cyanide attack. In the beginning, the structure of **396** was not clear but after purification on a silica column the corresponding cyclopentanone **398** was isolated, which could easily be identified.



It became obvious that no basic conditions could be used when working with the imines **38**. In order to introduce a cyanide group on the imine in acidic conditions, hydrogen cyanide was used.[186] This gas was generated by addition of hydrochloric acid to potassium cyanide. The gas was passed through a tube containing $CaCl_2$ (drying agent), through an empty flask and than bubbled into a cooled (0°C) solution of the imine in ether.

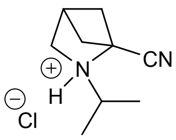


The exhaust was passed again through an empty bottle and then bubbled through 2 washing bottles containing a 6N NaOH solution. The exhaust was directly connected to the fume hood. A 5 to 10 fold excess of KCN was used since it was difficult to predict how many equivalents really condensed in the reaction mixture. Using the hydrogen cyanide gas a quantitative conversion to the amino nitriles was realised.



38a **100%** **399** (3/1 *cis/trans*) **400**

The amino nitrile **399** was obtained as a mixture of two isomers (3/1 *cis*/*trans*). It is obvious that only the *cis*-isomer can lead to the desired end product, namely the 2-isopropyl-2-azabicyclo[2.1.1]hexyl-1-carbonitrile **400**. When the ring closure of **399** was evaluated using a base such as triethyl amine or sodium hydride, a complex reaction mixture was always formed. The major compound in this mixture was in most cases the rearranged product **396**, so not only the imines were unstable in basic conditions but also the amino nitriles. Deprotonation of the N-atom led to expulsion of the cyanide group rather than to ring closure. The expulsion of cyanide is not new and has been described during the synthesis of 1-amino-2,2-dialkylcyclopropanecarboxylic acid.[187] This is a severe problem and therefore the ring closure was evaluated in neutral conditions without using base.



401

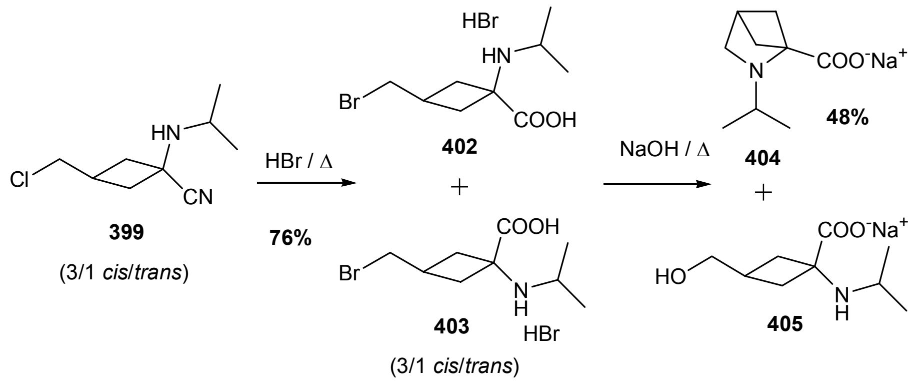
Heating the reaction in isopropanol for 1.5 hours was unsuccessful and all the starting product was recovered. When the product was heated for a longer period, *e.g.* overnight reflux, a very small amount of the end product **401** could be isolated as the hydrochloride salt (yield <5%).

Table 8: Evaluated reaction conditions for the ring closure of amino nitrile **399**

Base	Reaction conditions	Result
1.2 equiv. NEt_3	Δ THF/ 2 d	Complex reaction mixture
1 equiv. NEt_3	THF RT overnight	Complex reaction mixture
1.1 equiv. NaH	Δ THF / overnight	Complex reaction mixture
No base	Δ isopropanol/ 1.5 h	No reaction
No base	Δ isopropanol / overnight	Starting material + <5% **401**

4.6.3.3. Acid hydrolysis of the amino nitile **399** and cyclisation to 2,4-methanoproline derivatives

To avoid that the cyanide moiety acts as a leaving group, it was first hydrolysed to the carboxylic acid. The cyanide group was hydrolysed by refluxing the adduct **399** overnight in a concentrated hydrobromic acid solution (48% HBr in H_2O). On one hand the acid was obtained, but on the other hand the chloride atom was substituted by bromide. This is positive since a better leaving group will facilitate the subsequent ring closure.



By refluxing the obtained amino acid mixture in a sodium hydroxide solution, the methanoproline analogue **404** could be isolated in 48 % yield. The yield is rather low since the amino acid **402** was formed as a mixture of *cis*- *trans* isomers (3/1 *cis/trans*) and therefore the maximum yield of **404** is 75%. Also, some compound was lost during the crystallisation (methanol, water) to separate the two amino acids **404** and **405**.

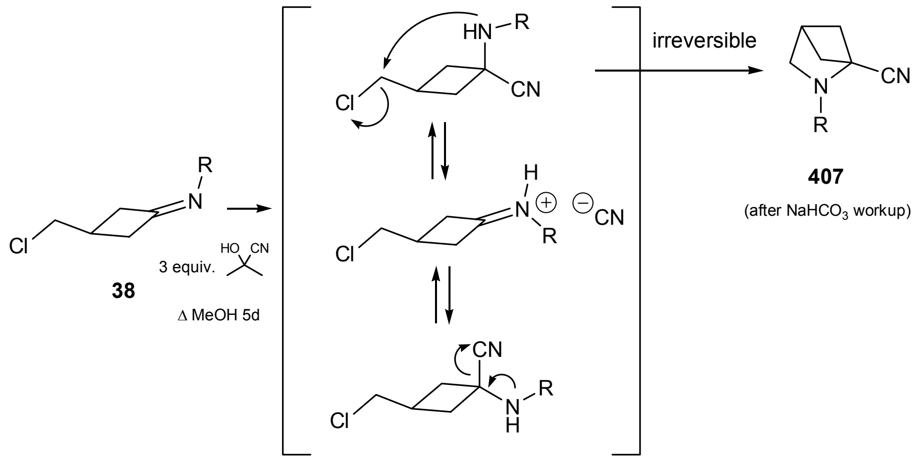
4.6.3.4. Optimised method for the synthesis of 2,4-methanoproline derivatives using acetone cyanohydrine

As can be concluded from the Table 8, it is not necessary to use a base to achieve ring closure. By refluxing the adduct **399** in isopropanol, a minor amount of bicyclic compound **401** was obtained. Another important remark is that only the *cis*-isomer can lead to the end product. But as can be deduced from the described experiment the cyanide group can also be kicked out, leading back to the imine and hydrogen cyanide gas. Bearing this information in mind, several experiments analysing the conditions that allow ring closure as well as isomerisation of the amino nitrile moiety were conducted. The boiling point of hydrogen cyanide gas caused a problem. The ring closure appears to take place at higher temperatures but the boiling point of HCN gas is only 26°C. Therefore, a precursor of the gas was used, *e.g.* acetone cyanohydrine. This compound, which is the hydrogen cyanide adduct of acetone, liberates the gas at higher temperatures.

Table 9: Evaluated reaction condition for the ring closure of **399**

Reagents	Reaction conditions	Result
1.2 equiv acetone cyanohydrine	Δ 65°C 18 h (MeOH)	Mainly imine **396**
1.2 equiv. acetone cyanohydrine 6 equiv. $NaHCO_3$	Δ 65°C / 3h	75% pure adduct **399**
3 equiv. acetone cyanohydrine 6 equiv. K_2CO_3	Δ 65°C / 24 h (MeOH)	Complex reaction mixture
6 equiv. acetone cyanohydrine 6 equiv. $NaHCO_3$	Δ toluene / 21 h	Complex reaction mixture
6 equiv. acetone cyanohydrine	Δ 65°C / 22 h (MeOH)	17% adduct **399** 13% end product **400** (after flash)
3 equiv. acetone cyanohydrine	Δ 65°C / 24 h (MeOH)	70% adduct **399** 30% end product **400** (from spectra)
3 equiv. acetone cyanohydrine 1.1 equiv. potassium cyanide	Δ 65°C / 24 h (MeOH)	50% adduct **399** 40% end product **400** (from spectra)
3 equiv. acetone cyanohydrine 1.1 equiv. potassium cyanide	Δ 65°C / 4d (MeOH)	Complex reaction mixture
3 equiv. acetone cyanohydrine	Δ 35°C / 2d (Et_2O)	Imine **396**
3 equiv. acetone cyanohydrine	Δ 65°C / 4d (MeOH)	50% end product **400** (after flash)
3 equiv. acetone cyanohydrine	Δ 65°C / 5d (MeOH)	68 % end product **400** (acid-base extraction)

From Table 9 it can be concluded that bases should be avoided even though they accelerate the adduct formation in an early stage. The best conditions to perform the ring closure as well as the isomerisation of the amino nitrile **399** were the use of 3 equivalents of acetone cyanohydrine and the reflux in methanol for 5 days without base. A convenience of this reaction is that no other side products could be detected. The reaction proceeds as follows: when refluxing is stopped after only 1 hour, the imine was totally converted to the adduct **399**. After heating for one day around 15% of end product can be detected in the crude spectrum together with the adduct **399** in a 3/1 ratio. After heating for 3 days, most of the starting material is converted to the end product but still a small amount of adduct is present in a 3/1 ratio. After a heating period of 5 days only the end product and some traces of the excess of acetone cyanohydrine could be detected. Thus, the ratio remained at 3/1 during the complete duration of the reaction and this is a very important fact. It means that the isomerisation is a rather fast reaction compared to the ring closure and it is of course the proof that isomerisation really takes place.



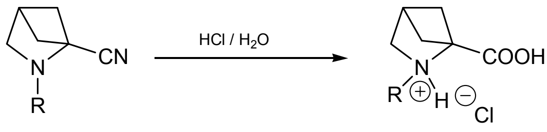
406

There are two ways to purify the reaction product. In fact it is better to say: “to remove the small excess of acetone cyanohydrine”. The first is column chromatography which has the disadvantage to be time consuming and expensive. Additionally, silica is polar and the 2-azabicyclo[2.1.1]hexanes also, which leads to a considerable loss of compound during purification. On the other hand, the nucleophilic N-atom is ideal to perform an acid/base extraction. In this way the excess of acetone cyanohydrine was removed and the isolated yield of the end product was improved considerably.

Table 10: Yields of the 2-alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile **407**

R=	Yield after flash chromatography	Yield after acid/base extraction
a) -iso-propyl	50 %	68 %
b) -t-butyl	40 %	50 %
c) -iso-butyl	56%	74 %
d) -allyl	55 %	78 %
e) -n-propyl	58 %	67 %
f) -benzyl	50 %	80 %

Hydrolysis of the nitrile group leads directly to the 2,4-methanoproline analogues **408** in good yield. This procedure to prepare for instance the iso-propyl compound **408a** is much better than the one previously described, because here all the isomers are converted to the end product and no unwanted product is formed.

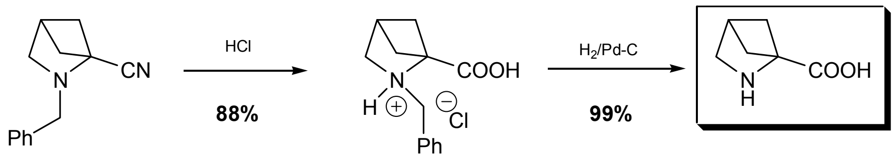


407 **408**

Table 11: Yields of the 2,4-methanoproline analogues **408**

R=	Yield
a) -iso-propyl	78 %
b) -t-butyl	68 %
c) -iso-butyl	82 %
d) -n-propyl	85 %
e) -benzyl	88 %

To obtain the natural amino acid, 2,4-methanoproline **3**, the alkyl substituent on N should be removed. First the t-butyl derivative **408b** was refluxed under drastic acidic conditions in the hope that not only the nitrile was hydrolysed but that the t-butyl group would be removed at the same time. Unfortunately this did not happen but it may be important to mention that no degradation of the hydrolysed compound **408b** was observed. This means that the 2-azabicyclo[2.1.1]hexane structure is very stable under acidic conditions. The natural 2,4-methanoproline **3** could be prepared by removal of the benzyl group of **407f** using classical catalytic hydrogenation. With an almost quantitative yield, the end product was obtained.

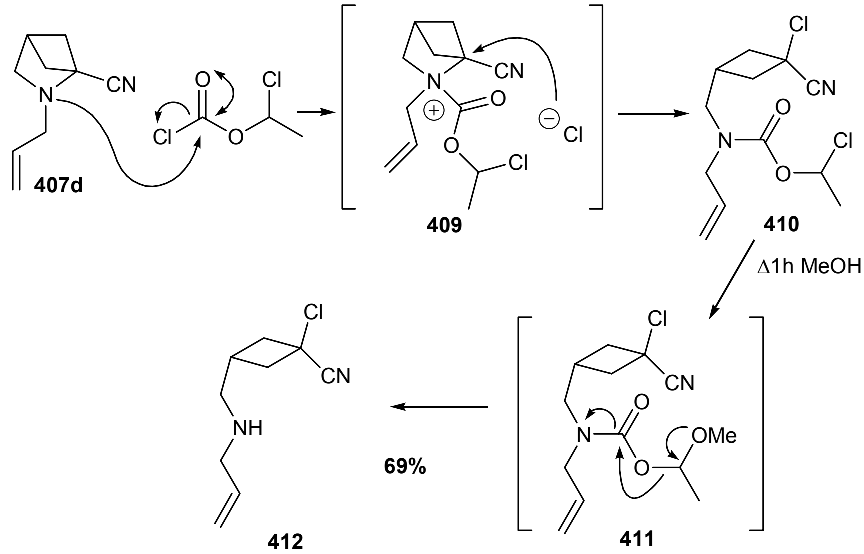


407f **408e** **3**

overall yield = 20%
6 steps

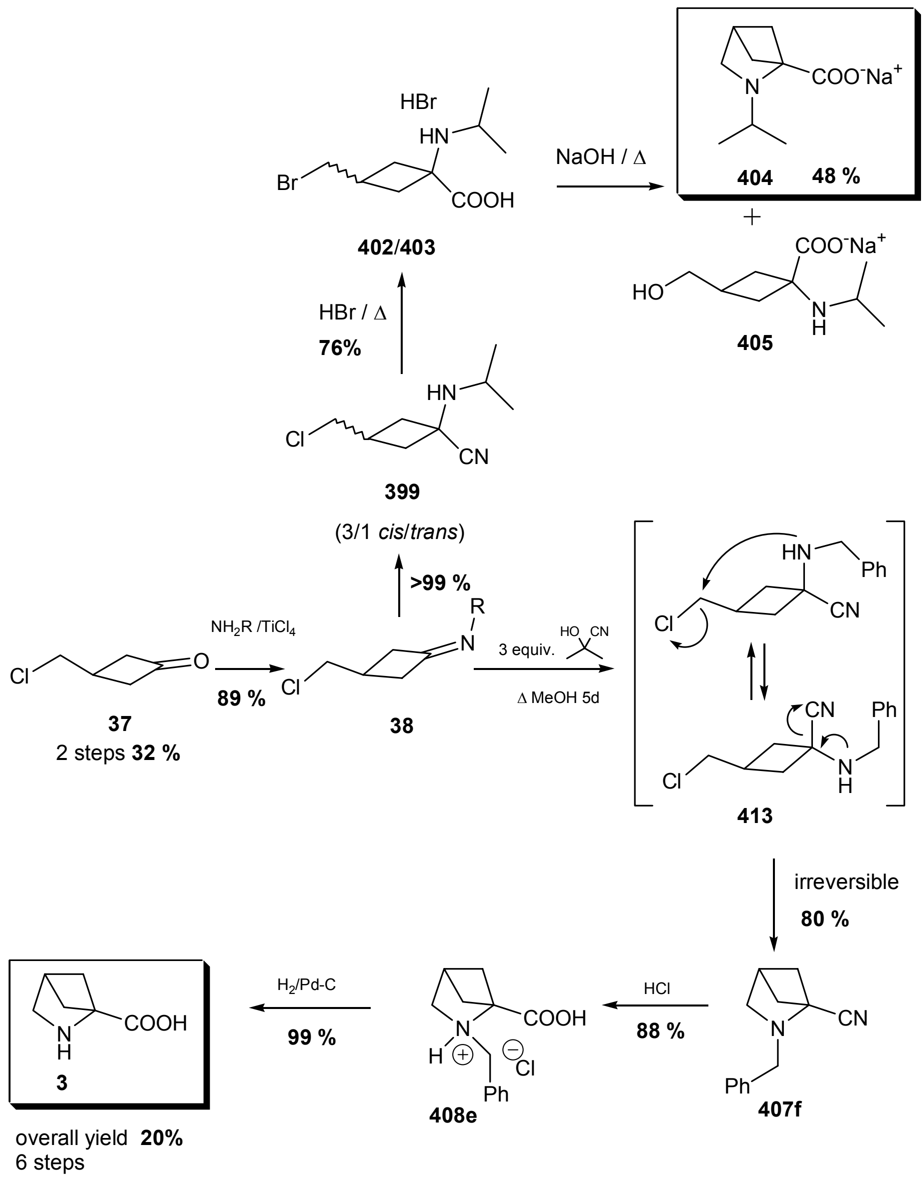
The natural amino acid **3** was synthesised in 4 steps in 62% yield starting from the 3-(chloromethyl)cyclobutanone.

The deprotection of an N-allyl group can be performed through different procedures.[188,189] The deprotection of **407d** was evaluated using ACE-Cl. Usually the bicyclic skeleton is very stable but using ACE-Cl led to ring opening and after workup the amine **412** was isolated in 69 % yield.


CN
O
Cl
Cl
O
407d
CN
O
O
Cl
Cl
409
Cl
CN
O
N
Cl
O
410
Δ1h MeOH
Cl
CN
NH
412
69%
Cl
CN
O
N
OMe
O
411

OVERVIEW 3

With this procedure the natural 2,4-methanoproline **3** could be synthesised in 6 synthetic steps with an overall yield of 20 %.



It is not only possible to hydrolyse the nitrile group but this function can also be reduced to the corresponding methylamines in very good yields using $LiAlH_4$. No side products were formed and purification proceeds by filtering off the aluminium salts over celite.

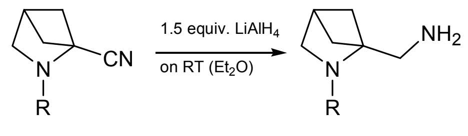
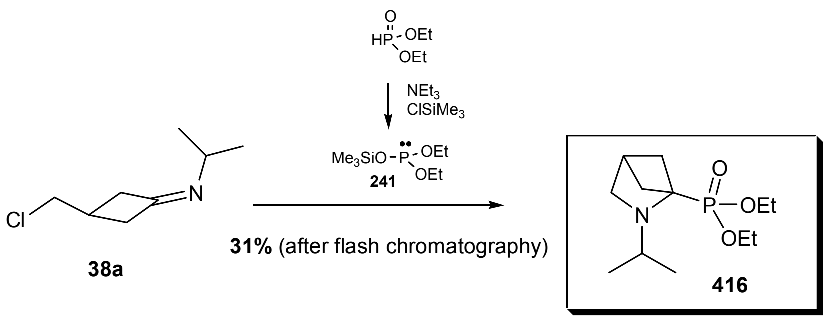


Table 12: Yields of the amines **414**

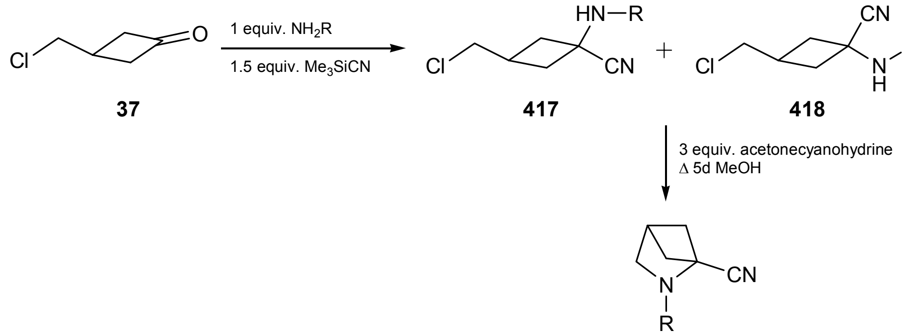
R=	Yield
a) -iso-propyl	78 %
b) -t-butyl	92 %
c) -iso-butyl	84 %
d) -n-propyl	91 %
e) -allyl	82 %

The ring closure was also evaluated with nucleophiles other than cyanide. Sodium azide and a phosphite reagent **415** were tested. In the case of the sodium azide, only complex reaction mixtures were obtained and no ring closed product could be isolated. Using the silylated phosphite reagent **415,** the bicyclic aminophosphonate **416** was isolated.



The crude reaction product was almost pure, but severe loss of compound occurred when performing column chromatography leading to a low yield (31%).

This methodology to synthesise the 2-azabicyclo[2.1.1]hexane skeleton starting from 3-(chloromethyl)cyclobutanone was very interesting, but in my opinion too long. Therefore, attention was focused to shortening the reaction pathway. When searching the literature, some procedures were found to synthesise amino nitriles directly from the ketone without first isolating the imines. After evaluation of some reaction conditions the amino nitriles **417**/**418** could be prepared in 1 step using trimethylsilyl cyanide and the appropriate amine.

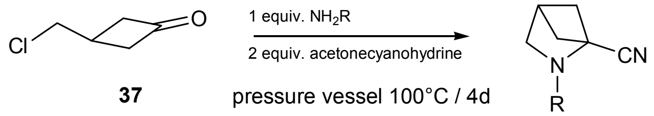


407

Table 13: Yields of the amino nitriles **417**, **418**

R=	Yield	Ratio **417**/**418**
a) -benzyl	99 %	73/27
b) -t-butyl	98 %	70/30
c) -iso-propyl	99 %	76/24

This reaction has an almost quantitative yield, no side products were formed and thus no purification was necessary. When these amino nitriles were dissolved in methanol and 3 equivalents of acetone cyanohydrine were added and heated for 5 days, almost the same yield for the ring closure was obtained. This means that the imine formation can be replaced with this very high yielding procedure. An even shorter procedure was developed as follows: the 3-(chloromethyl)cyclobutanone **37** was dissolved in dry methanol, 1.1 equivalent of amine, 2 equivalents of acetone cyanohydrine were added and this mixture was heated in a closed vessel for 4 days to give the bicyclic compounds with an even slightly better yield. Recently, it was seen that a heating period of 1 day is sufficient for the N-benzyl derivative **407e**.



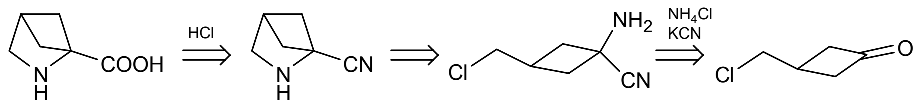
407 a) R = -*iso*-propyl **75 %**
e) R = -benzyl **83 %**

overall yield R = -*iso*-propyl 24%
R = -benzyl 26%

only 3 steps

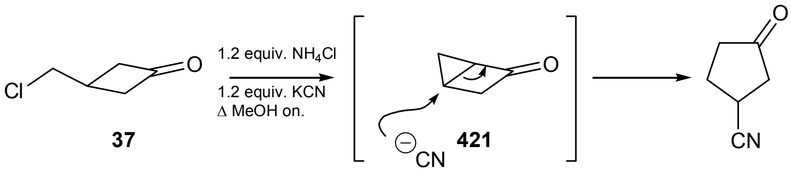
This is without any doubt the shortest and easiest synthesis of the 2-azabicyclo[2.1.1]hexane skeleton. In only three steps this very constrained skeleton can be prepared.

This pathway is very interesting but, to obtain the natural amino acid, the N-protecting group has to be removed in an additional step. Therefore, several other N-sources (ammonia, HMDS,[190] ammonium formate, ammonium acetate and ammonium chloride) were evaluated to avoid the deprotection step and shorten the sequence even more. In the initial experiments, the classical Strecker type conditions on the 3-(chloromethyl)cyclobutanone were used with the idea that the *in situ* formed amino nitrile **420** would lead to ring closure. This molecule could be converted in one step to the natural 2,4-methanoproline. This would not only be a short 4-step sequence, but also a rather inexpensive pathway to synthesise this amino acid.



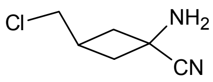
3 **419** **420** **37**

The first experiments were very disappointing. Using 1.2 equivalents of ammonium chloride and 1.2 equivalents of potassium cyanide (Δ MeOH, on.) led to the formation of the cyclopentanone **398** through an analogous bicyclic intermediate **421** as previously described.



37 **421** **398**

Some attempts were made to isolate this bicyclic intermediate **421** using bases such as NaH, LDA or LiHMDS[190] but none of these reactions led to the desired intermediate. To illustrate that potassium cyanide was causing this problem, the reaction was performed using only potassium cyanide and 3-(chloromethyl)cyclobutanone. This mixture in methanol was heated overnight and



420

the cyclopentanone **398** was indeed formed. When evaluating different reaction conditions, the observation was made that using an excess of ammonium chloride suppressed this unwanted side reaction. When 3 equivalents of ammonium chloride were used the adduct **420** could be isolated with a low yield of 29%.

Table 14: Reagents and reaction conditions evaluated on 3-(chloromethyl)cyclobutanone **37**

Reagents	Reaction conditions	Result
1.2 equiv. NH_4Cl 1.2 equiv. KCN	Δ 65°C / on.	Cyclopentanone **398**
NH_3-solution 1.2 equiv. KCN	RT / on.	Complex reaction mixture
3 equiv. KCN	Δ 65°C / on.	Cyclopentanone **398**
1.1 equiv. NEt_3 1.2 equiv. KCN	RT / 3d	Complex reaction mixture

2.2 equiv. KCN	RT / 3d	Cyclopentanone **398**
3 equiv. NH_4Cl 1.1 equiv. KCN	RT / 3d	29 % adduct **420**
3 equiv. NH_4Cl 1.1 equiv. KCN	RT / 7d	Adduct **420** + side products
3 equiv. NH_4Cl 1.1 equiv. KCN	Δ 65°C / 1d	Complex reaction mixture

Because of the complexity of this reaction, the reaction conditions were first optimized for the synthesis of the adduct **420**. One of the possibilities to prepare amino nitriles was the use of trimethylsilyl cyanide. Several N-sources and different conditions were evaluated to perform the reaction.

Table 15: Reagents and reaction conditions evaluated on 3-(chloromethyl)cyclobutanone **37** with the formation of the amino nitrile **420**

Reagents	Reaction conditions	Ratio **420**/**37**
1 equiv. NH_3 (7N NH_3 in MeOH) 2 equiv. Me_3SiCN	3 h RT cool to 0°C + Me_3SiCN on. RT	6/1
2 equiv. $HCOONH_4$ 2 equiv. Me_3SiCN	3h RT cool to 0°C + Me_3SiCN on. RT	20/1
2 equiv. $HCOONH_4$ 2 equiv. Me_3SiCN	7h RT cool to 0°C + Me_3SiCN 3d RT	22/1
2 equiv. NH_3 2 equiv. Me_3SiCN	3h 0°C + Me_3SiCN on. RT	10/1
7N NH_3 in MeOH as solvent 2 equiv. Me_3SiCN	1h 0°C + Me_3SiCN RT on.	3/1
2 equiv. NH_4OAc 2 equiv. Me_3SiCN	3h RT cool to 0°C + Me_3SiCN on. RT	11/1
2 equiv. NH_4Cl 2 equiv. Me_3SiCN	2h 30 RT cool to 0°C + Me_3SiCN on. RT	4/1
1.5 equiv. $HCOONH_4$ 2 equiv. Me_3SiCN	2h 30 RT cool to 0°C + Me_3SiCN on. RT	26/1

1.5 equiv. $HCOONH_4$ 2 equiv. Me_3SiCN	2h 30 RT cool to 0°C + Me_3SiCN on. RT Δ reflux 1d	Complex reaction mixture
2 equiv. NH_3 (7N in MeOH) 2 equiv. Me_3SiCN	1h 0°C + Me_3SiCN on. RT	Complex reaction mixture
7N NH_3 in MeOH as solvent $Ti(OiPr)_4$* 1.5 equiv. Me_3SiCN	5 h RT cool to 0°C + Me_3SiCN on. RT	Complex reaction mixture
1.2 equiv. HMDS 1.5 equiv. Me_3SiCN	4h 30 RT cool to 0°C + Me_3SiCN on. RT	6/1
HMDS as solvent 2 equiv. Me_3SiCN	2h RT + Me_3SiCN 5h RT then Δ on.	1/10
5 equiv. NH_3 2 equiv. Me_3SiCN	Δ 120°C on. closed vessel	Complex reaction mixture

* ref.[191]

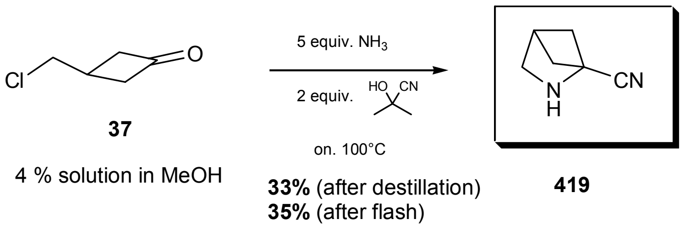
The ratio of adduct **420** to starting material **37** is given in Table 15. The best N-sources to prepare the adduct were ammonium formate or ammonium acetate. The only problem using this procedure was the purification. In the H-spectrum of the crude mixture, almost no starting material was present and the formed adduct **420** was pure except for the presence of ammonium acetate or formate. Several attempts were undertaken to remove these compounds by performing an acid/base extraction, but in all cases the product broke down to some extent. The adduct could however be isolated by filtering the crude mixture over a very short silica column (2 or 3 cm) and washing it thoroughly with dichloromethane. Ring closure was not observed in any of the used conditions. It is rather logical that ring closure is more difficult on the adduct **420** compared to **399** where an alkyl group is present on the N-atom. This alkyl group makes the N-atom more nucleophilic and thus facilitates the ring closure. For this reason some experiments were performed using HMDS as N-source.[190,192] In these cases the trimethylsilyl group is not only electron donating but is also very easy to remove afterwards. Unfortunately, no very good results were obtained. Also at elevated temperatures, no ring closure could be detected and only complex reaction mixtures were obtained.

The adduct **420** could be synthesised using acetone cyanohydrine as cyanide source. The advantage was that higher temperatures could be used which did not automatically lead to degradation. Table 16 gives a summary of the results.

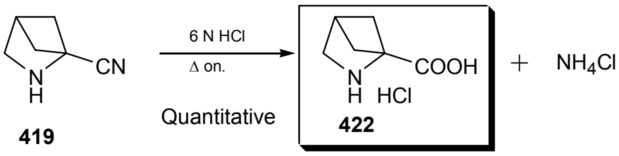
Table 16: Reagents and reaction conditions evaluated on 3-(chloromethyl)cyclobutanone **37**

Reagents	Reaction conditions	Ratio **420**/**37**
3 equiv. NH_4Cl 3 equiv. acetone cyanohydrine	(methanol as solvent) Δ reflux 1d	No reaction
HMDS as solvent 2 equiv. KCN	Δ reflux overnight	No reaction
HMDS as solvent 3 equiv. acetone cyanohydrine	Δ reflux 1d	13/1
5 equiv. NH_4Cl 5 equiv. acetone cyanohydrine	Solvent (MeOH/H_2O 1/1) Δ reflux overnight	75/1 no ring closure
5 equiv. NH_4Cl 5 equiv. acetone cyanohydrine	Solvent (MeOH/H_2O 1/1) Δ reflux 7d	Complex reaction mixture Mainly starting material
5 equiv. NH_3 (in MeOH) 2 equiv. acetone cyanohydrine	Δ 100°C overnight pressure vessel	Ring closure to **419**
1.5 equiv. HMDS 2 equiv. acetone cyanohydrine	5 % solution in MeOH Δ 120°C overnight pressure vessel	Ring closure
2 equiv. NH_3 (in MeOH) 1.5 equiv. acetone cyanohydrine	solution in MeOH Δ 120°C overnight pressure vessel	Small amount of ring closure
5 equiv. NH_3 (in MeOH) 1.5 equiv. acetone cyanohydrine	solution in MeOH Δ 70°C overnight pressure vessel	Complex reaction mixture
7N NH_3 as solvent 3 equiv. acetone cyanohydrine	Δ 70°C overnight pressure vessel	Complex reaction mixture
2 equiv. NH_3 (28-30% in water) 2 equiv. acetone cyanohydrine	Δ 120°C overnight pressure vessel	Complex reaction mixture
1.5 equiv. NH_3 (in MeOH) 1.5 equiv. acetone cyanohydrine	Δ 100°C toluene overnight	Complex reaction mixture
5 equiv. NH_3 (in MeOH) 5 equiv. acetone cyanohydrine	Δ 120°C overnight presser vessel	Complex reaction mixture

In most cases, basic conditions are not compatible with the adduct **420**, but still an amount of base needs to be present for the ring closing step. When only ammonium chloride and acetone cyanohydrine were used in a mixture of methanol/water 1/1 (reflux overnight), the cyclobutanone **37** was almost completely converted to the adduct **420**. Using these conditions, refluxing the mixture for 7 days led to a reaction mixture which consisted mainly of starting material and no ring closure took place. When 5 equivalents of ammonia (7N solution in MeOH) and 2 equivalents of acetone cyanohydrine were heated together with 3-(chloromethyl)cyclobutanone at 100°C in a pressure tube, the desired bicyclic amino nitrile **419** was formed and could be isolated. A little amount of a different unidentified compound was present and the crude end product was distilled under high vacuum.



This was the ideal precursor of 2,4-methanoproline. The nitrile group of **419** was hydrolysed by refluxing it in a 6N hydrogen chloride solution overnight. The compound was quantitatively converted to the natural 2,4-methanoproline. This is a very short and rather cheap 4 step sequence to this amino acid.



2,4-Methanoproline

The yield for **419** was still low and therefore the search was continued. Several other conditions were evaluated using lithium perchlorate to stimulate the imine formation step and/or ultrasonic conditions to reduce the reaction time. The results are described in Table 17.

Table 17: Reagents and reaction conditions evaluated on 3-(chloromethyl)cyclobutanone **37**

Reagents	Reaction conditions	Ratio **420/37**
5M $LiClO_4$ in Et_2O as solvent 1.5 equiv. HMDS 2 equiv. acetone cyanohydrine	1.5h 0°C + acetone cyanohydrine ultrasonic bath 45°C overnight closed vessel	Adduct but no ring closure
1.5 equiv. HMDS in Et_2O 2 equiv. acetone cyanohydrine	1h 0°C + acetone cyanohydrine Ultrasonic bath 45°C overnight	Pure starting material
1.5 equiv. HMDS in MeOH 2 equiv. acetone cyanohydrine	Ultrasonic bath (45°C) overnight	3/1 adduct/starting material
1M $LiClO_4$ in Et_2O 1.5 equiv. HMDS 2 equiv. acetone cyanohydrine	3 h RT + acetone cyanohydrine Δ 105°C overnight pressure vessel	Complex reaction mixture
5M $LiClO_4$ 1.5 equiv. HMDS	1d RT	4/1 imine/ starting material **37** (by **IR**-spectrum)
5 equiv. NH_4Cl 2 equiv. NH_3 in MeOH 5 equiv. acetone cyanohydrine	MeOH/ H_2O 1/1 Δ 100°C overnight pressure vessel	Ring closure to **423**
5 equiv. NH_4Cl 5 equiv. acetone cyanohydrine	Δ 100°C overnight pressure vessel	Reaction mixture

The imine formation step was followed using IR spectroscopy. When the 3-(chloromethyl)cyclobutanone **37** was dissolved in a 5M solution of $LiClO_4$ in diethyl ether and was stirred at room temperature, the intense peak of the ketone decreased while a new peak was formed around 1650 cm^{-1}. After stirring for 5 hours, an estimated conversion of 50% was noticed. When the reaction was stirred overnight, this ratio improved to 75%.

The most interesting reaction conditions are marked in Table 17. When **37** was heated with a combination of 5 equivalents of ammonium chloride, 2 equivalents of ammonia and 5 equivalents of acetone cyanohydrine in a mixture of water and methanol (1/1) at 100 °C overnight, a different compound was formed. At first it looked as if compound **419** was formed. A closer look at the H spectra indeed revealed that some peaks had shifted slightly. When the carbon spectrum was collected big differences arose.

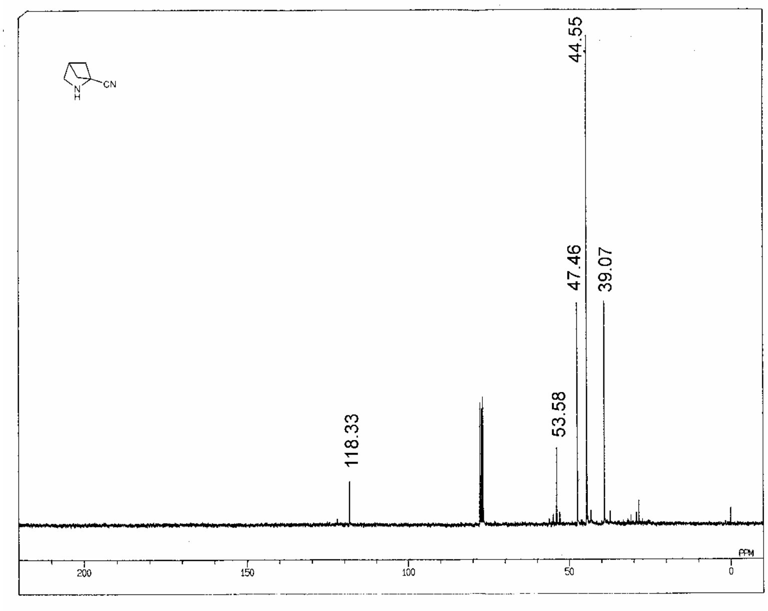


Figure 3: ^{13}C-spectrum of compound **419**.

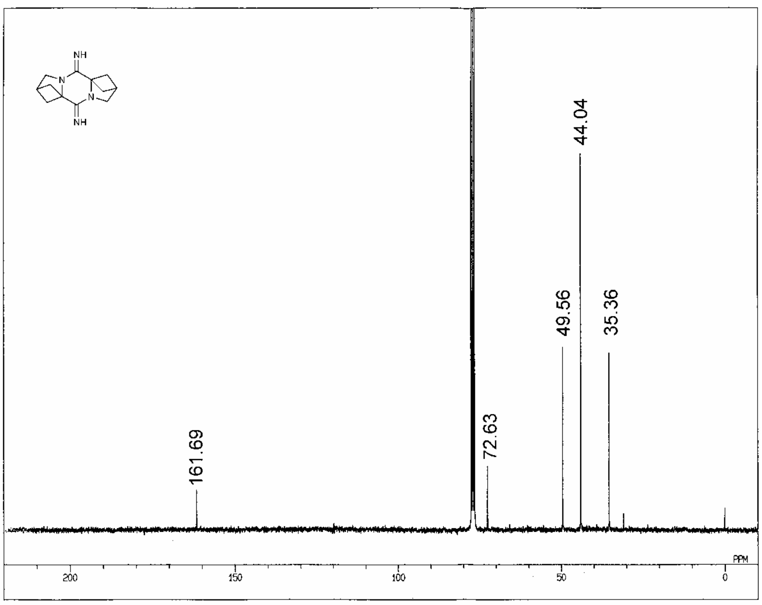
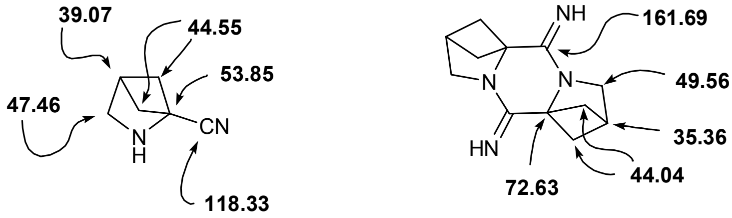


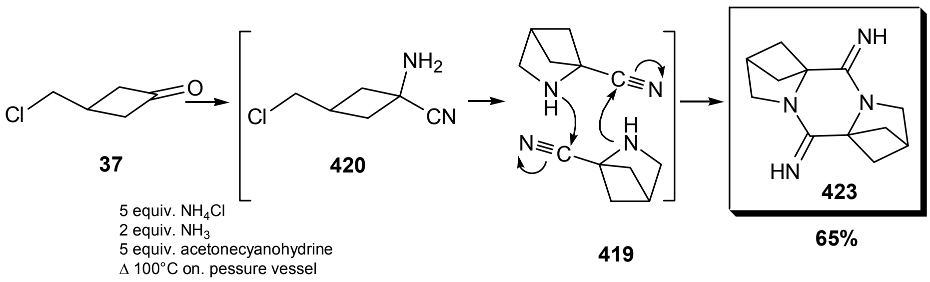
Figure 4: ^{13}C-spectrum of compound **423**

There was no cyano-group in the compound but instead a peak at 161.69 ppm was present. Also in the infrared spectrum no nitrile could be detected but an intense peak was present around 1653 cm^{-1}. Apart from this, the value for the quaternary carbon was much higher than expected. This carbon was at 72.63 ppm instead of 53.85 ppm in **419**. There were only 5 different C-atoms present and except for the quaternary atom, the other carbon atom values were similar. For this reason it was thought that the structure was analogous, but with another functional group present instead of the nitrile. An amide group seemed a possibility, but the electrospray mass spectrum (positive mode) revealed a single peak at *m/z* 219, corresponding to a molecular mass of 218.

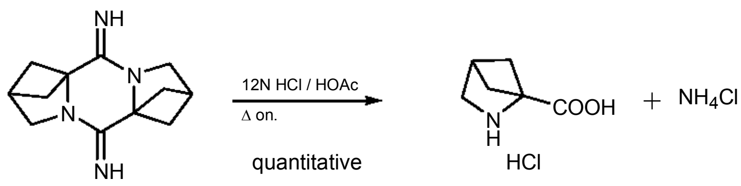


419 **423**

Collecting the mass spectrum using a GC-MS apparatus gave the same result: 219 (M^++1, 14, ^{13}C contribution corresponding to 12C), 218 (M^+, 100), (for other fragments see experimental part). With all this information we were rather sure that the isolated compound was a dimer, even better a symmetrical dimer since only 5 different C-atoms were present. Therefore, the compound was assigned the pentacyclic structure **423** because all the spectra fit with the proposed structure. It was probably formed with the desired compound **419** as intermediate.



Although this was not the compound aimed at, **423** is also a precursor of the natural 2,4-methanoproline. This compound proved to be rather stable in acid medium and drastic condition had to be used to hydrolyse it to the amino acid.

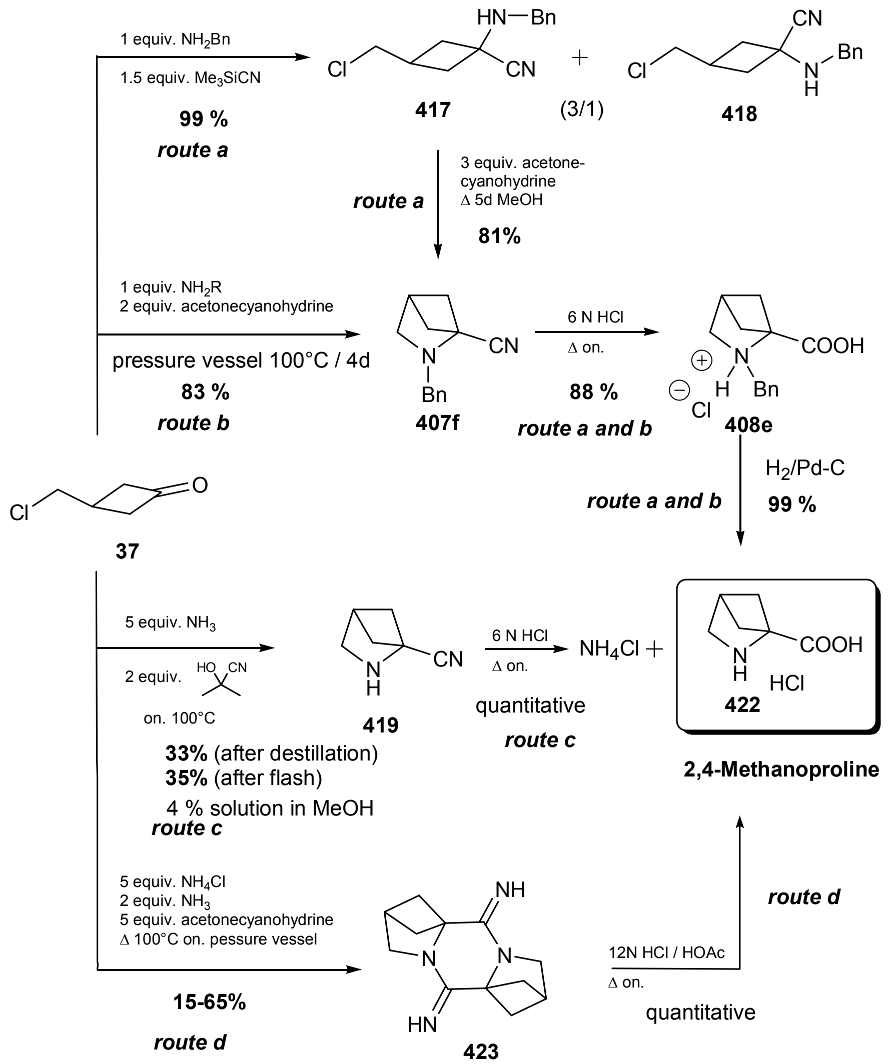


423 **422**

Through this 4 step sequence, 2,4-methanoproline was synthesised with an overall yield of **21 %**.

OVERVIEW 4

In this overview several pathways and shortcuts to synthesise 2,4-methanoproline are given. Other pathways have already been described in overviews 1 and 3.



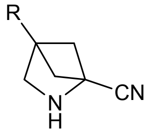
(2 steps for the preparation of 3-(chloromethyl)cyclobutanone **37**)

Route a: 6 steps; overall yield = 22 %
Route b: 5 steps; overall yield = 23 %
Route c: 4 steps; overall yield = 11 %
Route d: 4 steps; overall yield = 21%

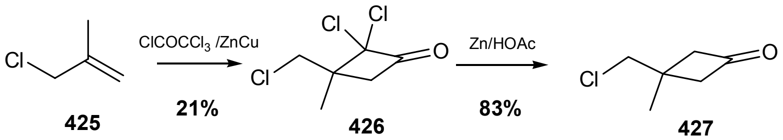
Route b is up to now the preferred pathway for the preparation of 2,4-methanoproline. This is a 5 step sequence, the reaction is very reproducible and can be performed on gram scale.
In route c and d 2,4-methanoproline was prepared in only 4 steps. Route c is however the most promising pathway since this reaction is reproducible and the crude reaction mixture contains 60 % of end product **419**. Due to the polar nature of this compound the yield after purification is low (35 %). If the formation of **419** could be improved by changing the reaction conditions, the purification would be easier and a higher yield would be obtained.
Route d is also very interesting but the reaction was difficult to reproduce. The compound **423** was formed in all cases but the isolated yield varied from 15 % up to 65 %.

4.6.4. Attempted synthesis of C4 substituted 2-azabicyclo[2.1.1]hexanes

As described above the 2-azabicyclo[2.1.1]hexane skeleton could be synthesised starting from 3-(chloromethyl)cyclobutanone **37**. Allyl chloride was used to prepare this cyclobutanone. An analogous pathway was evaluated using methallyl chloride as starting material. If the reaction proceeds, 2-azabicylo[2.1.1]hexanes could be synthesised with a substituent on the two bridgehead carbons. The cycloaddition of methallyl chloride with dichloroketene, generated from trichloroacetyl chloride and a Zn/Cu couple, proceeds only with a very low yield (21%). The two geminal chloride atoms could be removed using zinc in refluxing acetic acid.

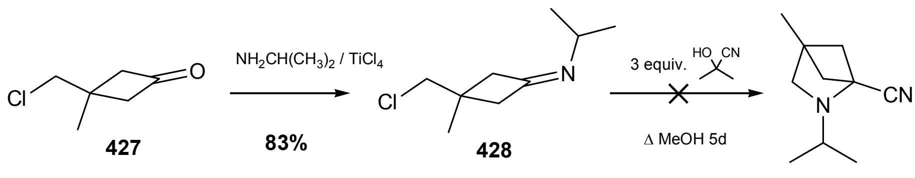


424



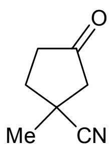
425 **426** **427**

In this way the cyclobutanone **427** was obtained in good yield (83%). The synthesis of the imine caused no problems and the compound **428** was isolated in 83 % yield.

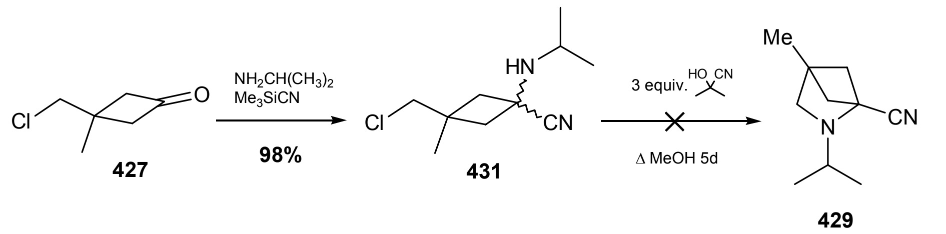


429

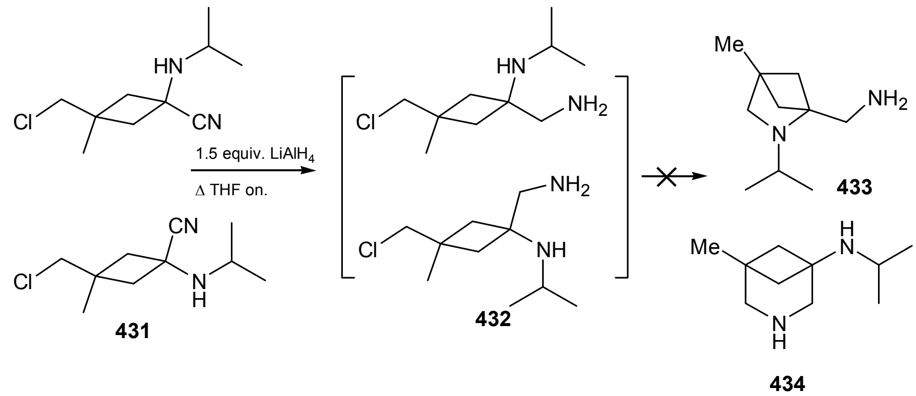
Unfortunately using the optimal reaction conditions (for the ring closure of the imines derived from 3-(chloromethyl)cyclobutanone **37**) did not lead to the bicyclic compound **429**. After purifying the reaction mixture, only the rearranged product **430** could be isolated. This was a rather unexpected result and was therefore further investigated. To analyse the reaction, the amino nitrile **431** was synthesised first. This was prepared starting from the ketone, adding isopropyl amine and trimethylsilyl cyanide. The amine nitrile was almost quantitatively obtained (yield = 98%). When this compound was treated under the same conditions for ring closure, a complex reaction mixture was obtained. Because the adduct **431** was formed in a 45/55 ratio of isomers, the ring closure will take more time.



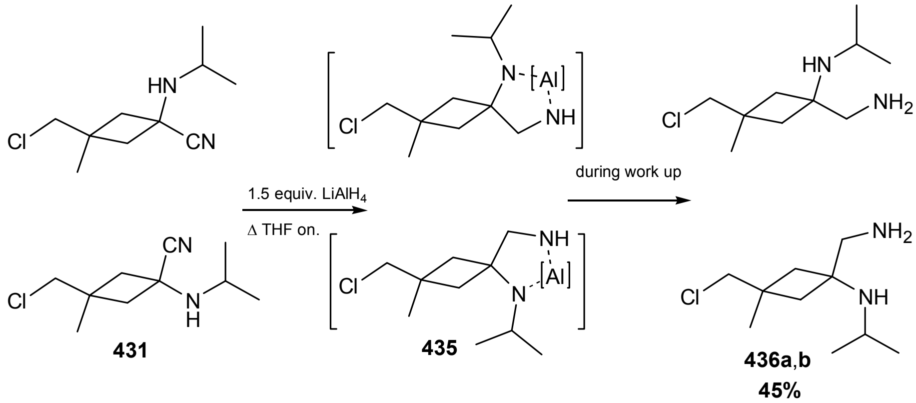
430



Since it was not clear what caused the formation of a rather complex reaction mixture, the amino nitrile **431** was reduced with lithium aluminumhydride in the hope that the two obtained isomers would ring close.



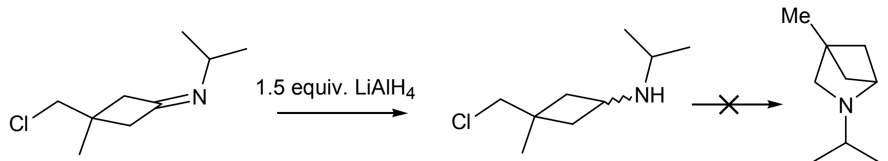
The *cis*-isomer would lead to the 2-azabicyclo[2.1.1]hexane skeleton **433** and the *trans*-isomer to the 3-azabicyclo[3.1.1]heptane skeleton **434**. The used conditions normally lead to ring closure, but here no ring closure was observed. Nevertheless, the nitrile group was reduced to the methylamine **436a**,**b**. It is very strange that under these conditions also the *trans*-isomer did not close to compound **434** since here the energy needed to form the additional 6-membered ring would be a lot less than to construct the 2-azabicyclo[2.1.1]hexane skeleton. One possibility to explain this result is that during the reduction of the nitrile group the aluminium is complexed with the other amino group present in a 5-membered ring. It is possible that this complex is stable during the reaction and that it prevents the ring closure.



431 435 436a,b 45%

The complex could then decompose during the workup and lead to the production of the free amines **436a**,**b**. To avoid this complexation, the amines **436** were deprotonated using sodium hydride to evaluate the ring closure, but the reaction led to a mixture of compounds and it was impossible to determine the structure of these compounds.

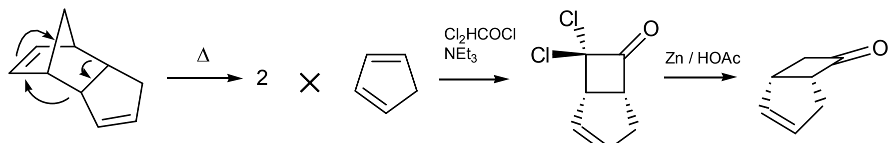
On the other hand the imine **428** was reduced with lithium aluminium hydride to form the 2-azabicyclo[2.1.1]hexane skeleton. Unfortunately, again no ring closure was observed and the amine **437** was isolated in 24% yield. A possible explanation for the difficulty in cyclising **432** and **437** is the unfavourable eclips interaction between the CH_2Cl bond and the C-CH_3 bond in the transition state during the internal S_N2 reaction.



428 24% 437 438

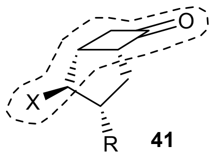
4.7. Synthesis of the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton

The successful pathway to prepare 2-azabicyclo[2.1.1]hexanes used the 3-(chloromethyl)cyclobutanone **37** as starting material. It would be interesting to know if this procedure could be applied to synthesise more complex and even more constrained molecules.

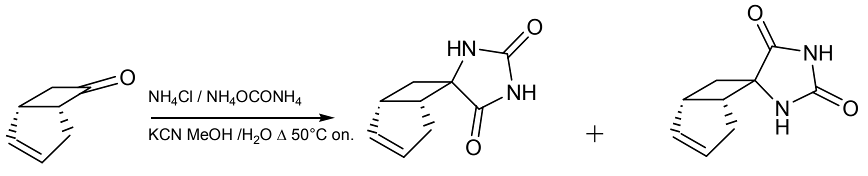


439 440 200 40

To prepare tricyclic molecules one should start from a suitable bicyclic compound which is easy to synthesise. The bicyclic ketone **40** was chosen as precursor since the double bond could be halogenated which could finally lead to ring closure. Further, the bent structure could lead to an improved ratio of isomers by a favourable exo-attack. The bonds that are indicated in **41** show the similarity with the previous pathways. This cyclobutanone **40** is a known molecule in literature and can be synthesised on a very large scale starting from the cheap dicyclopentadiene. Following generation of cyclopentadiene from its dimer dicyclopentadiene via retro-Diels Alder reaction, this reacts rapidly with dichloroketene, generated from dichloroacetyl chloride and triethyl amine. Dehalogenation using zinc in acetic acid affords the bicyclic starting material. The aim was to synthesise a tricyclic amino acid with a very constrained structure. Therefore, the hydantoin was prepared from the cyclobutanone **40**. The procedure for the preparation of the hydantoin was similar as for the preparation of **360**, but the result was somehow different. In both cases, a mixture of diastereoisomers was obtained and in the case of **179** the mixture was very difficult to separate. Only a fractional crystallisation was successful and the yield after separation was very low (only 20%). In the case of **40** this was very different. During the reaction, a white powder precipitated from the reaction mixture (which was also the case with **360**) but only one of the two diastereoisomers crystallised.

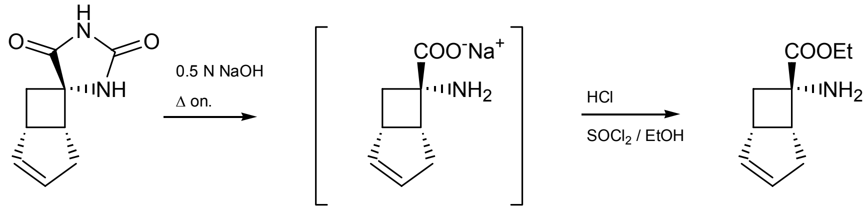


41



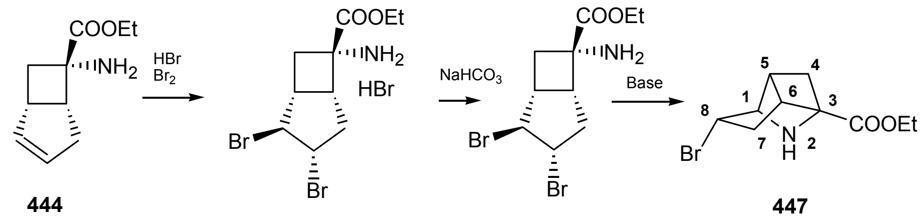
40 72 % **441** **442** **61 %** pure *cis*-isomer

The temperature appeared to be an important parameter. Performing the reaction at room temperature led to long reaction times (up to 7 days to reach completion). Temperatures above 50°C should however be avoided since the isolated yield of the end product decreases. Workup and analysis of the reaction mixture showed that it was the major isomer which crystallised selectively from the reaction mixture. This major isomer was found to be the endo-compound **442** formed through the preferential exo-cyclic attack of cyanide on the *in situ* formed imine. Through a straightforward filtration of the suspension, a first fraction of 50% **442** could be obtained. After workup of the remaining mixture, the isomers could be crystallised leading to another fraction of 11 % of the desired diastereoisomer. The remaining supernatant (11%) was still a mixture of the two diastereoisomers. The hydantoin **442** was further converted to the amino acid **443** by heating with a 0.5N sodium hydroxide solution. After a period of reflux of 13 hours (overnight), the hydrolysis was completed and the amino acid **443** was obtained in pure form and could be used without purification in the next step. No other organic compounds were present although sodium carbonate was left in the end product. To remove this and other inorganic salts, the amino acid was converted to the amino ester. The ester is soluble in dichloromethane and all the inorganic salts were removed in the water phase during the extraction. The ethyl ester was prepared using thionyl chloride in absolute ethanol. Basic workup led to the isolation of the ethyl ester **444** in 53% yield.



442 **443** **53 %** (from **442**) **444**

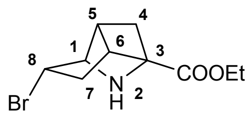
In the next step the amino group was protected *in situ* as a hydrobromide salt during the bromination. Usually the salt is deprotected during workup, but it was observed that the salt of the brominated end product crystallised selectively. After the reaction dry ether was added to improve the salt formation and the suspension was filtered.



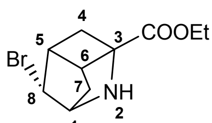
444 **445** **446** **447**

The hydrobromide salt was not hygroscopic and after drying under high vacuum the white powder could be stored at room temperature for months. This compound was totally pure and no further purification was needed. The bromination was completely diastereoselective and only compound **445** was formed.

The stereochemistry was proved by performing the ring closure first and analysing the tricyclic compound. Theoretically, two possible structures could have been formed, these are **447** or **448**. The bromonium ion is formed diastereoselectively (exo), and is opened regioselectively at the sterically more accessible endo C-position to form **447**. Compound **448** would result from internal displacement of the diastereoisomeric dibromo compound **446’** originated from the endo attack of bromide on the less accessible C-position. The

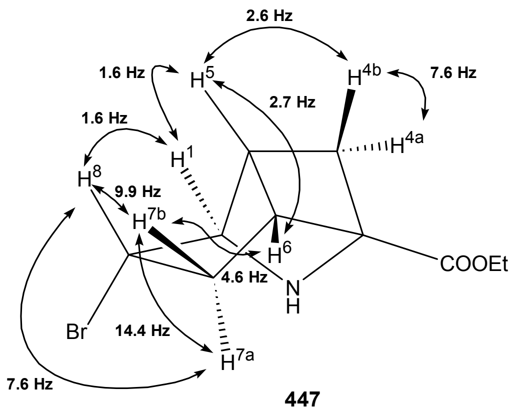


447



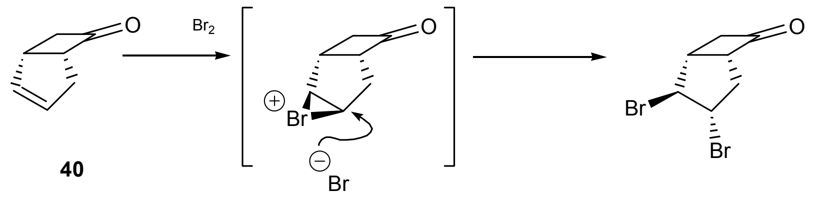
448

numbering of compound **447** is according to the UPAC numbering but compound **448** is numbered in analogy with **447** and not according to the IUPAC numbering. After deprotection of the ammonium salt by $NaHCO_3$ extraction, the free amine was ring closed using 1 equiv. of triethylamine. The structure of **447** was proved by determination of all the couplings constants and studying the H-H cosy and H-C HETCOR spectra. In these spectra a clear coupling between the H^8 and both H^{7a} and H^{7b} can be observed. Proton H^8 also couples with H^1. This means that the remaining C<u>H</u>Br proton, which can indistinguishably be assigned, couples with a CH and both protons of a CH_2. This can only be the case in compound **447**. Supplementary proof for the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton can be obtained by comparing the coupling constants with the predicted ones. Since the molecule is very constrained, a good prediction of the torsion angles can be derived from a 3D-computer model (ACD/ 3D, version 4.02). Proton H^{7a} should not couple with proton H^6 due to a torsion angle of 88.4° which is in agreement with the Karplus equation stating that the coupling constant is close to zero. In the case of structure **448** there is no direct reason why the two protons of CH_2 7 would not couple with H^6. Also proton H^{4a} does not couple with H^5. The prediction of the torsion angle is here around 73°. The geminal coupling between H^{4a} and H^{4b} is rather small, only 7.6Hz. This is in agreement with the coupling constants in 2-oxabicyclo[2.1.1]hexane and the 2-azabicyclo[2.1.1]hexane skeleton.



447

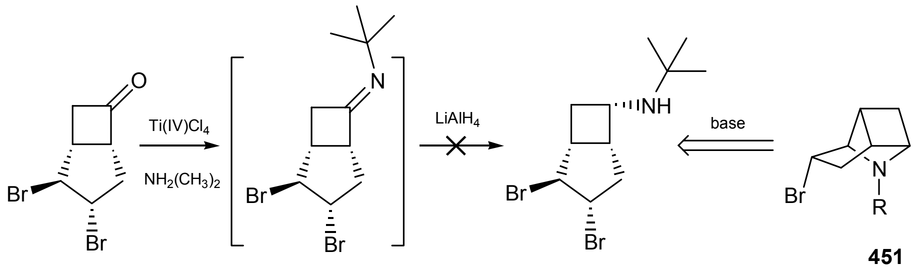
This pathway was extended to make different derivatives with the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton. Therefore, attempts were performed to synthesise the imines of the cyclobutanone **202**. The bromination of **40** is described in literature and this reaction proceeds both stereo- and regioselectively. The selectivity can be explained by looking at the transition state **201**. Because of steric reasons, the bromonium ion is formed exo-cyclic. For the same reason the bromide ion attacks endo on the indicated carbon atom.



40 201 202

This is important because it is only the exo oriented bromide that can be substituted in a SN_2 fashion by an endo-oriented amino group.

The synthesis of the imine **449** was evaluated using titanium(IV)chloride under standard conditions but this always led to a complex reaction mixture. In standard conditions, the ketone is mixed together with the amine and the titanium(IV)chloride (dissolved in a small amount of pentane) is added dropwise at 0°C. The inverse addition was also evaluated. In this case the ketone was mixed with the titanium(IV)chloride and the amine is added dropwise. This procedure sometimes gives better results, especially when the amine is causing side reactions. However, also in this case, side products were formed along with the imine **449**. Bromide, being a good leaving group, probably caused these side reactions that led to complicated mixtures.

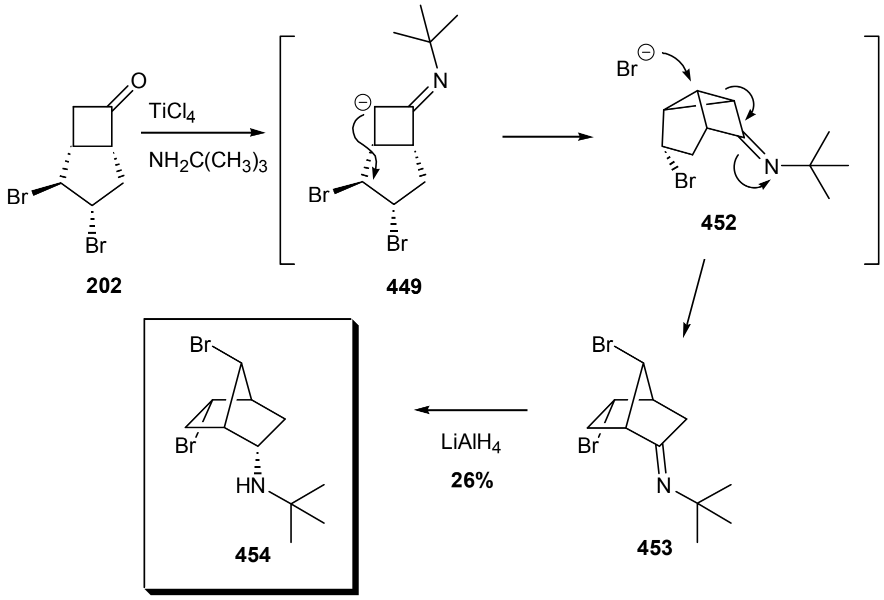


202 449 450 451

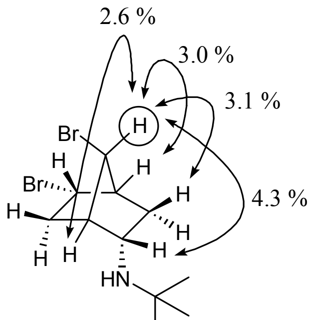
When performing the reaction at low temperature (-78°C) for a short time (1h), the imine **449** was formed. However, this compound proved to be very unstable and except for the H and C spectra, no other spectra could be collected. The spectra are very complex since the imine was formed as a mixture of E/Z-isomers and some traces of side products were present.

The imine was directly reduced after preparation, using lithium aluminium hydride to evaluate the ring closure to the tricyclic compound **451**. Hydride should preferentially attack from the exo-phase leading to a mixture of mainly the endo oriented amine **450**. Only the exo-oriented bromide atom can be substituted intramolecular by the endo-oriented amine leading to the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton. Unfortunately a very complex reaction mixture was obtained and the reaction was repeated at room temperature rather than refluxing in THF. Even in this case a mixture was obtained. The reaction was purified by column chromatography and only traces of what was presumably amine **450** were obtained. Because this was only a small amount

(26%), the structure and especially the stereochemistry were uncertain. The isolated compound proved to be rather stable. When heating this unknown compound with 1 equivalent of sodium hydride during an overnight period no reaction took place and the starting material was completely recovered. The spectral data however indicated that two bromide atoms and a NH-group were still present. Because of the importance of this compound the structure was thoroughly analysed. The structure appeared to be the norbornene **454** instead of the desired amine **450**.



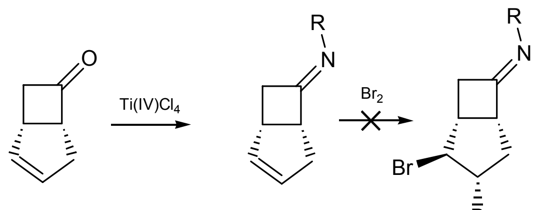
This structure was confirmed with DEPT, H-H COSY, DFQCOSY, H-C COSY, HMBC and NOE-experiments. In the last, the C$\underline{H}$Br (C7) was irradiated and an energy transfer was observed to the two bridgehead protons, $CH_{3a}\underline{H}_{3b}$ and the C$\underline{H}$NH-*t*Bu protons. This observation confirms structure **454** and can not be explained by structure **450**. Probably a rearrangement of the imine **449** took place during the imine formation step. Enolisation in α-position of the imine lead to the tricyclic structure **452** which undergoes a ring expansion to **453**. This imine was subsequently reduced by $LiAlH_4$ leading to the norbornene structure **454**. Probably the desired imine **449** was also reduced but this did lead to a complex reaction mixture. After purification by column chromatography only the stabile compound **454** was isolated.



455

Several analogous ring expansions have been described on the ketone **202** which confirms the reaction pathway and tricyclic intermediate **452**.[193,194,195,196]

The difficulty in preparing the imine **449** proved to be the presence of the bromide atoms. To avoid this problem, an alternative pathway was studied. The imines were prepared directly from the ketone **40** prior to bromination.

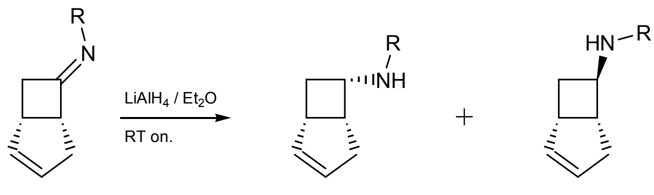


40 **456** **457**

Table 18: Yields of the isolated imines **456**

R=	Yield
a) -iso-propyl	95 %
b) -n-propyl	95 %
c) -t-butyl	84 %
d) -iso-butyl	89 %

The bromination of these imines was evaluated to compare the spectra of these compounds with those obtained above (compare **449** with **457**) to get an idea about the stereochemistry of the bromination. No conclusions could be drawn since a complex reaction mixture was obtained. Therefore, the imines were reduced before performing the bromination step. Lithium aluminium hydride was used as reductant and the amines were obtained as a mixture of diastereoisomers. The yield of the reaction was good, but depending on the alkyl group the separation of the two diastereoisomers was difficult. The amines are quite polar and have a high affinity for silica. This fact in combination with the difficult separation explains the moderate yield of the pure diastereoisomer.

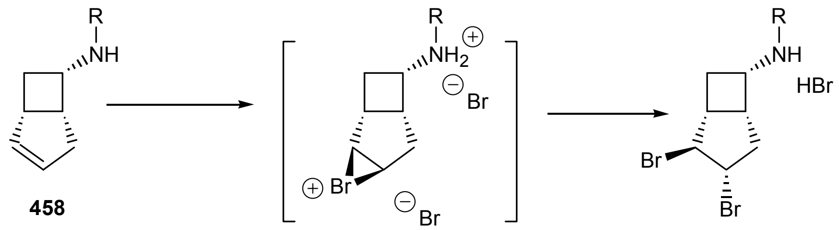


456 **458** **459**

Table 19: Yields of the isolated amines **458** and **459**, obtained after reduction of the corresponding imine **456**

R=	Yield *cis*-isomer **458**	Yield *trans*-isomer **459**
a) -iso-propyl	53 %	Not isolated
b) -n-propyl	44 %	Not isolated
c) -t-butyl	84 %	3 %
d) -iso-butyl	66%	6 %

The *cis*-isomer is of interest since this is the only isomer that can lead to a tricyclic skeleton. During the bromination step, the amino group was protected as a hydrobromide salt. In a classical bromination reaction the amine is protected, using HBr, bromine is added and afterwards the reaction is extracted with a sodium bicarbonate solution to neutralise the acid. In this particular case, the bromination was performed in dichloromethane and during the reaction a white powder precipitated from the reaction mixture. After stirring the mixture overnight, some dry ether was added to improve the salt formation and the suspension was filtered and washed thoroughly with dry ether. This procedure applies for all the evaluated compounds **461**.



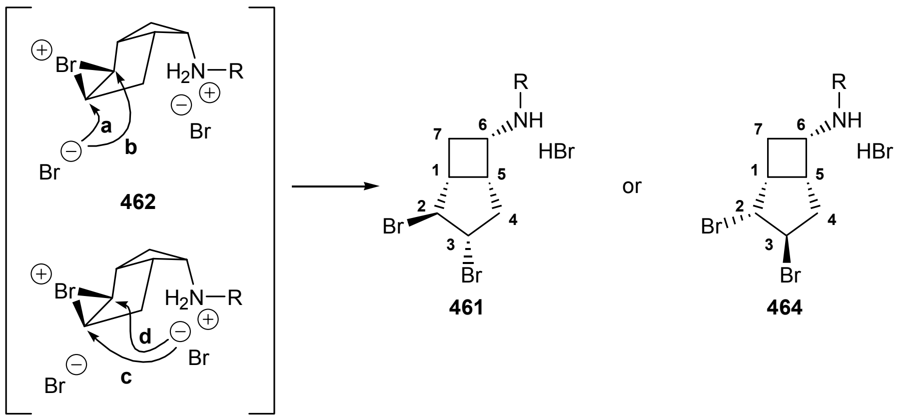
458 **460** **461**

When the filtrate was evaporated, only small amounts of starting material could be retrieved but no end product was present. The white powder that remained on the filter was the pure hydrobromide salt of the end product and no hydrobromide salt of the starting material was present. Many hydrobromide or hydrochloride salts are hygroscopic and are difficult to handle, but these compounds were not. After drying under high vacuum, the white powders were very stable and easy to handle. When kept in a closed vessel, they remain stable for months at room temperature and no degradation occurs. This is very convenient and because of the easy purification, the yields are high.

Table 20: Isolated yields of the brominated hydrobromide salts **461a,b,c,d**

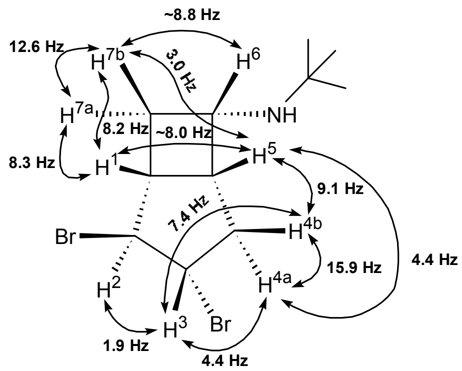
R=	Yield
a) -iso-propyl	95 %
b) -n-propyl	76 %
c) -t-butyl	80 %
d) -iso-butyl	81 %

An important issue in this reaction is the regioselectivity of the bromination. The reaction is somehow more complex than the bromination of ketone **40**. Also here, bromide can open the bromonium salt through route **a** or **b**. Route **a** is expected since the bromide attacks from the less-hindered side of the molecule. However, one might assume that the bromide atom from the hydrobromide salt opens the bromonium complex from the endo-phase of the molecule since the ammonium group is already endo oriented (route **c** or **d**). After performing the bromination reaction it was uncertain whether the compound had structure **461** (route **a** or **c**) or **464** (route **b** or **d**).



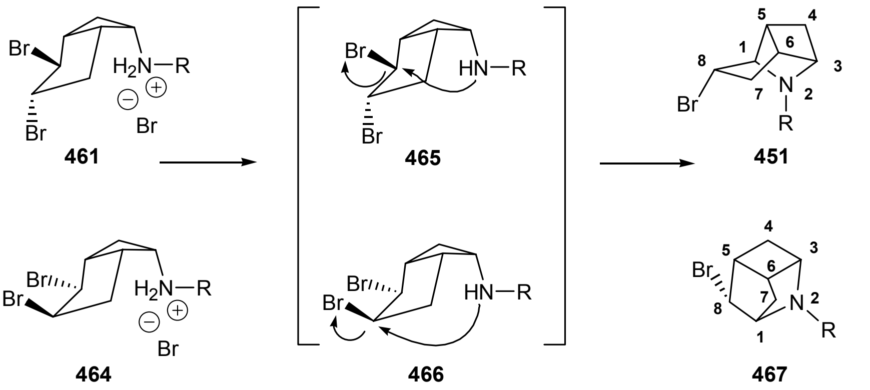
463

All the assignments of the protons could be made by looking at the coupled spectra (H-H; H-C). Unfortunately through the couplings constants no conclusions could be drawn concerning the stereochemistry. The ring closing step was performed first, since then two different compounds would be obtained and it would be easier to determine the structure. Therefore, the hydrobromide salt was deprotected after extraction with sodium bicarbonate. The resulting amines were not so stable and had to be used the same day because degradation proceeded spontaneously at room temperature. Only the t-butyl derivative **465c** was sufficient stable to determine all the coupling constants by performing different HOMO-experiments.

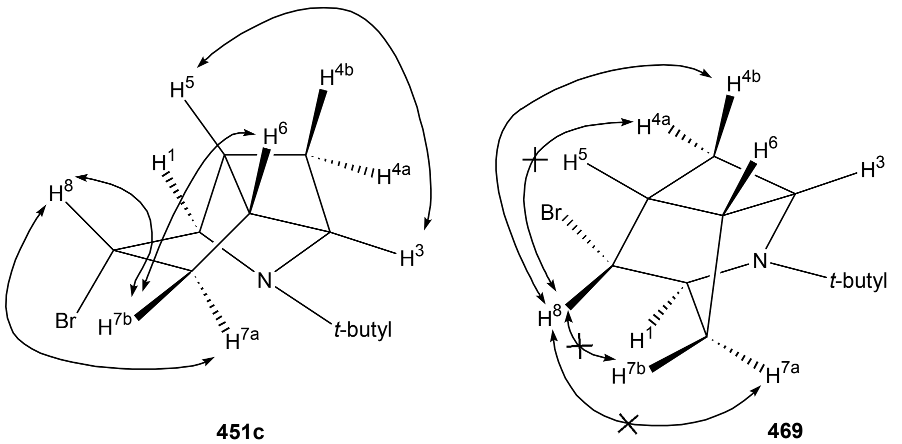


465c

The ring closure was evaluated with several bases including NaH, KOtBu, LDA and triethyl amine. In most cases a mixture of compounds was obtained except for the weaker base triethyl amine. Refluxing the amines **465/466** with 1 equivalent of triethyl amine in acetonitrile during an overnight period led to a pure ring closed product.



Only the exo-oriented bromide atom be substituted intramolecularly and this would lead to one of the tricyclic compounds **451** or **467**. Another method to prepare these tricyclic compounds used 2 equivalents of triethylamine directly added to the hydrobromic salt **461/464** and these were heated under reflux in acetonitrile for one night. The advantage was that deprotection and ring closure were done in the same step, but the disadvantage was that small traces of side product were present. When the deprotonation was performed in a separate step, the side product was not formed. The spectra were thoroughly analysed to determine wether the structure was **451** or **469**. Only the t-butyl derivative **451c** will be discussed since the other alkyl derivatives were analogous.



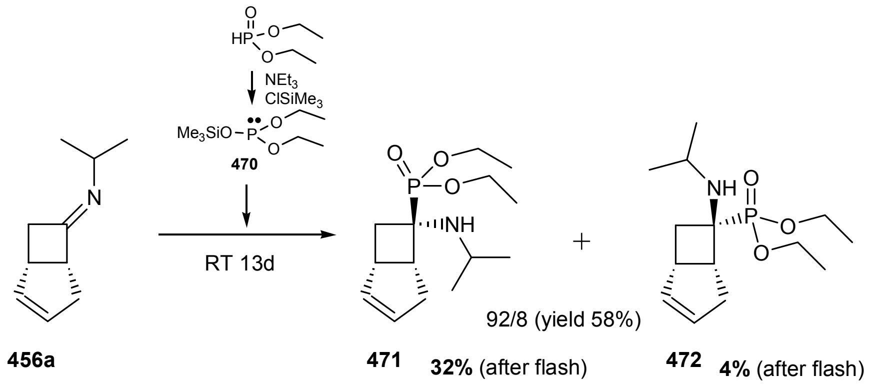
Some remarkable couplings can be seen in the H-H spectrum which result from the structure **451c**. The numbering of the protons in compound **469** is done in analogy with structure **468** and is not the IUPAC numbering. The H^8 proton which is at the the brominated carbon can be assigned without any doubt and starting from this proton the other protons were assigned. The H^8 proton couples clearly with the 2 protons of a CH_2 system. In structure **451c** this is H^{7a} and H^{7b}. In the other structure **469** there is no reason to believe that this proton can couple with both H^{7a} and H^{7b}. It could however show a coupling with H^{4b} through a W-coupling but not with H^{4a}. On the other hand only one proton, probably H^{7b} couples with H^6. This is possible and can be fully understood when a 3D-model is analysed. The tricyclic structure is very constrained and therefore a 3D-model can give a good prediction of the torsion angles. The torsion angle between H^{7a} and H^6 is almost perfectly 90° and the Karplus equation states that the predicted coupling constant is then close to zero. In the case of **469**, no reason can be found why H^{7a} and H^{7b} would not couple both with H^6. Another remarkable coupling is present due to the constrained structure. Proton H^3 couples with proton H^5 and this is because of the perfect W-conformation. All this information, together with the mass spectrum, which clearly shows the presence of only one bromine atom, led to the conclusion that **451c** is the correct structure. To our knowledge, this is the first synthesis of the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton.

The ring closure was evaluated using different alkyl substituents on the N-atom and the tricyclic compounds were isolated in good yields.

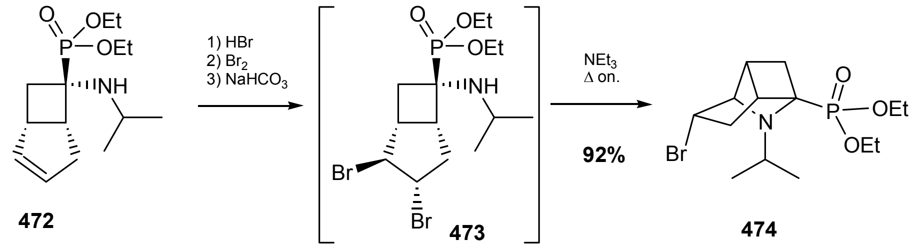
Table 21: Isolated yields of the tricyclic compounds **451a,b,c,d**

R=	Yield
a) -iso-propyl	81 %
b) -n-propyl	61 %
c) -t-butyl	72 %
d) -iso-butyl	84 %

This interesting pathway was further extended using nucleophiles other than hydride. After addition of the silylated phosphite **470** to imine **456a**, the amino phosphonate **471/472** could be prepared. This compound was obtained as a mixture of diastereoisomers (92/8) which were separated by column chromatography. Also in this case, only the *cis*-stereoisomer is of interest and was further used in the next step.

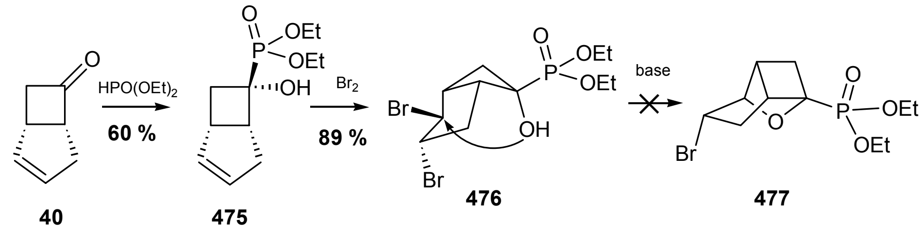


The formation of the aminophosphonate was a very slow reaction: it took about 2 weeks at room temperature to reach completion. The reaction could be accelerated by refluxing the mixture in dichloromethane but the disadvantage was the formation of some side products. When the reaction was performed at room temperature, no side products were formed and an acid/base extraction was used to remove the excess of phosphite reagent. The adduct was isolated with a yield of 58%, but after the separation of the two diastereoisomers the yield of the desired *cis*-isomer dropped to 32%. During the bromination step the free amine was protected as a hydrobromide salt through a procedure as described above. Unfortunately, the brominated hydrobromide salt did not crystallise and could not be isolated since it was very hygroscopic and therefore very difficult to handle. The brominated compound **473** could be isolated after an alkaline workup, but the compound had to be used immediately in the next step because it was very unstable and rapidly degradating at room temperature.



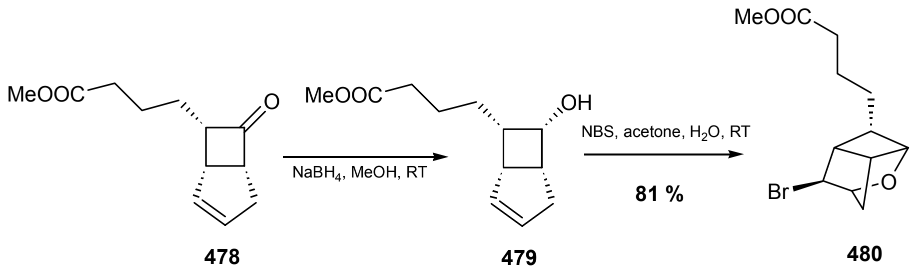
The ring closure could be performed by adding 1 equivalent of triethyl amine and heating the mixture overnight in acetonitrile. The tricyclic compound **474** was obtained as a pure product in very good yield. Since this methodology worked for the synthesis of aminophosphonates, it was further developed by one of the thesis students.[197] Several other derivatives were prepared, and the results are described in this Master thesis and are not further discussed here.

As mentioned in the literature part some examples of the 2-oxatricyclo[3.2.1.0^{3,6}]octane or the 2-oxatricyclo[3.3.0.0^{3,6}]octane skeleton have been described. One of our goals was to prepare phosphorus derivatives containing one of these two basic skeletons. The bicyclo[3.2.0]hept-2-en-6-one **40** was chosen as starting material.



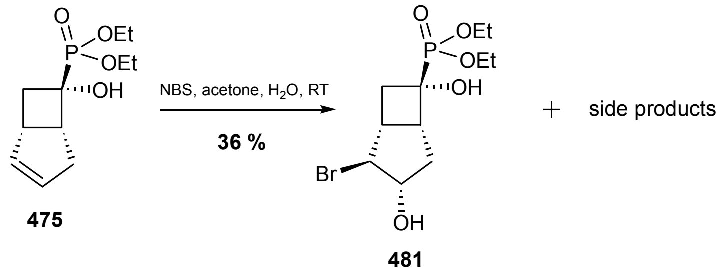
Hydroxyphosphonate **475** was prepared by heating the cyclobutanone **40** with an equal amount of diethyl phospite during an overnight period. The major *trans* isomer was isolated in a yield of 60 % (after purification by means of flash chromatography). This compound was brominated to **476** in excellent yield (89%) and no side products were formed during the bromination reaction. It was thought that deprotonation of the endo-oriented alcohol would lead to the desired 2-oxatricyclo[3.3.0.0^{3,6}]octane skeleton. Despite the efforts using bases such as NaH, LDA, LiHMDS under different reaction conditions (reflux in THF, or at -78°C), no tricyclic compound could be isolated. In all cases where the reaction was heated, a complex reaction mixture was obtained. At low temperature, either there was no reaction and the starting material was recovered or a degradation of the starting material occurred.

One very interesting reaction had been reported in literature for the preparation of the 2-oxatricyclo[3.2.1.0^{3,6}]octane skeleton using an intramolecular bromoetherification.



The cyclobutanone **478** was first reduced using $NaBH_4$ in methanol to obtain the alcohol **479** and its diastereoisomer in a ratio of 7:1 (the endo-alcohol was the major diastereoisomer). This compound **479** was subsequently treated with NBS in aqueous acetone resulting in the tricyclic compound **480** with a yield of 81 %.[198]

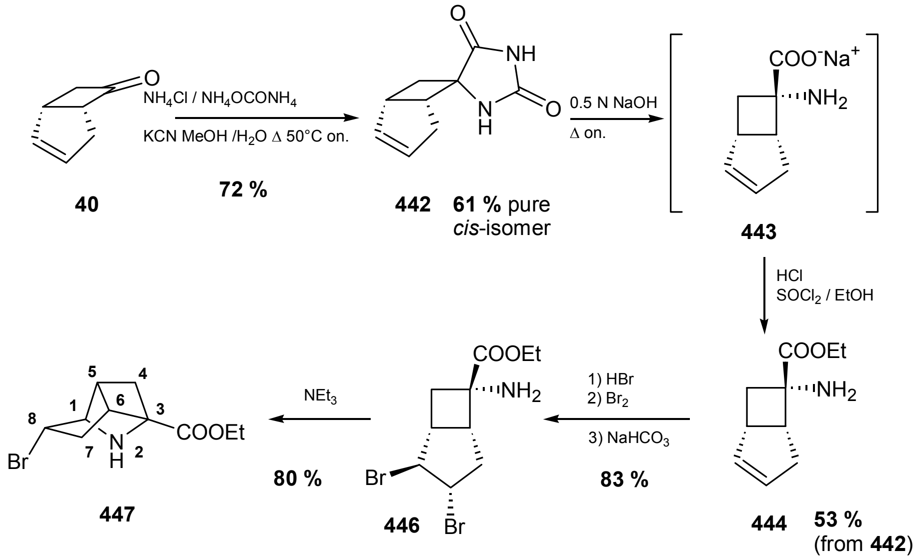
Treating the hydroxyphosphonate **475** under the same conditions as described in the literature gave a mixture of compounds that was separated by flash chromatography (EtOAc/MeOH 98/2).



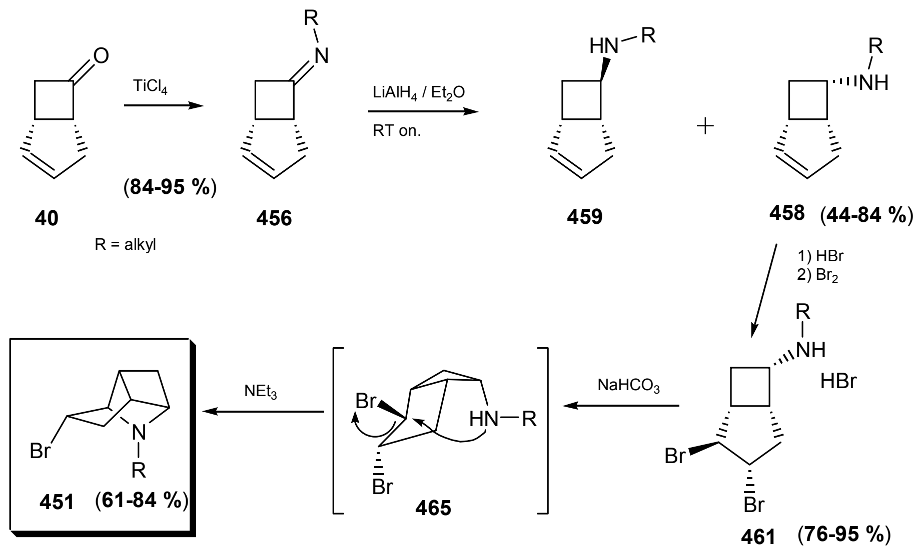
One spot with R_f = 0.24 could be isolated in pure form and appeared to be the phosphonate **481** (36 %). The other spot R_f = 0.33 could not be obtained in pure form and the structure could therefore not be determined.

OVERVIEW 5

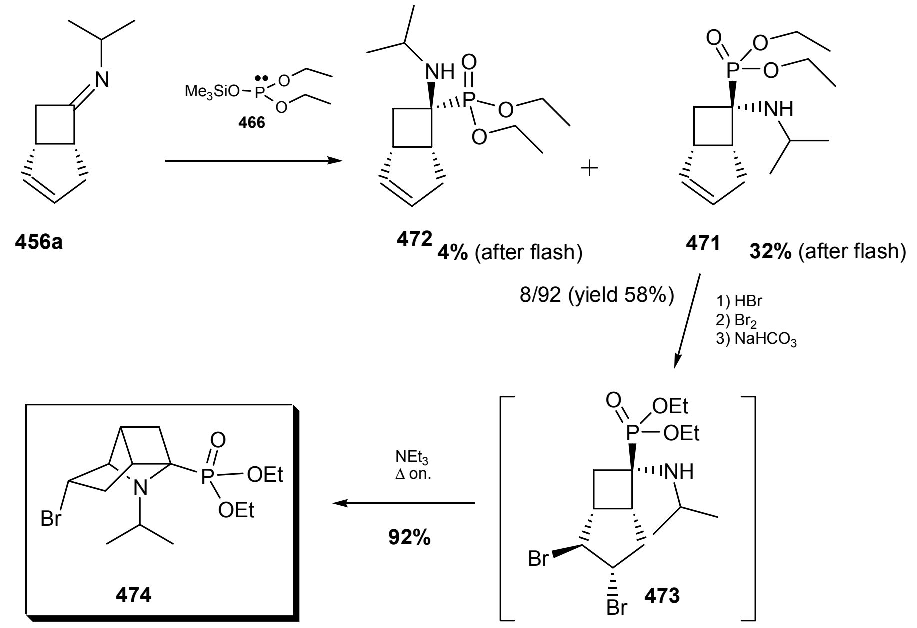
The tricyclic amino ester **447** was synthesised in 5 steps starting from the bicyclic ketone **40**. This compound contains the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton.



This pathway was extended for the synthesis of the tricyclic amines **451** and the tricyclic amino phosphonate **470**. Both structures were prepared by addition of a nucleophile (hydride or phosophite reagent **466**) and the imine **452**.



After separation of the two diastereoisomers obtained the endo-oriented amines **458** and **471** were brominated and ring closed to obtain the tricyclic compounds **451** and **474**.

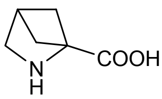


5. Biotesting

5.1. Introduction

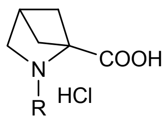
Several methods were developed to produce the 2-azabicyclo[2.1.1]hexane skeleton, 2,4-methanoproline, and its derivatives. Since the isolation of 2,4-methanoproline from seeds, an anti-feedant property was attributed to this compounds although real proof for this biological activity was lacking. Therefore the activity of methanoproline **3**, N-alkyl analoges **408**, cyano-analogues **407** and **414** were evaluated in an insect bioassay. Up to now, the biological activity of methanoproline **3** only was evaluated in a bioassay using a small rodent as test organism. The rejection of the seeds containing 2,4-methanoproline could not be explained by the sole presence of 2,4-methanoproline. The rejection of the seeds by insects on the other hand was never investigated.

2,4-Methanoproline was prepared through the hydantoin route whereas the preferred method for the production of the cyano and the aminomethyl derivatives was the addition–intramolecular substitution sequence. Using the methods described above, methanoproline **3** and methanoproline derivatives **408**, **407** and **414** were prepared in pure form for the *in vivo* testing of activity. The derivatives evaluated are shown below.



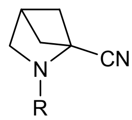
3

natural
2,4-methanoproline



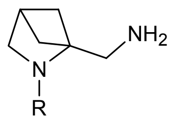
408

R = -iso-propyl
R = -t-butyl
R = -iso-butyl
R = -n-propyl



407

R = -iso-propyl
R = -t-butyl
R = -iso-butyl
R = -n-propyl



414

R = -iso-propyl
R = -t-butyl
R = -iso-butyl
R = -n-propyl
R = -allyl

5.2. Insect bioassays

Pure compounds were tested for insect repellent activity against larvae of the cotton leaf worm, *Spodoptera littoralis* (Boisduval) (Lepidoptera: Noctuidae). This is a major herbivorous insect pest of cotton, vegetables and ornamentals in Europe, the Mediterranean region and Northern America. Levels of resistance to classical insecticides and novel insecticide groups have been reported[1]

For the experiments, young (0-2 d old) last (6th)-instar larvae were selected from a continuous culture that was kept at standard conditions of 23±2°C, 65±5 % RH and a 16:8 (L:D) photoperiod as described previously.[199]

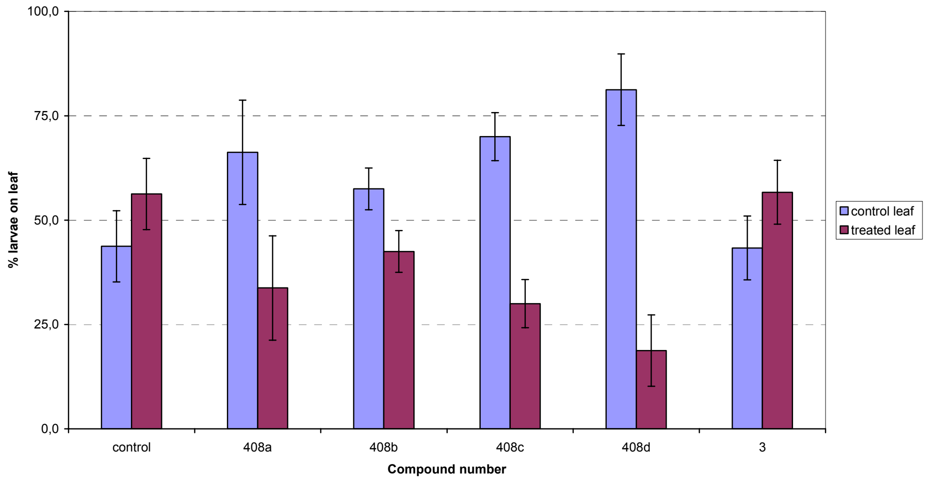
In a first screening bioassay with all compounds, a 0.1% solution was made in distilled water (compound **3**-**408**) or acetone (compound **407-414**).[200] Freshly cut castor bean leaves, *Ricinus communis L*., were sprayed uniformly on the upper side with 4 ml of solution in a standardized Cornelis' potter tower.[201] For controls, the leaves were treated with distilled water or acetone. After solvent evaporation in a fume hood, the leaves were placed in a 35 x 23 cm plastic canister with the treated leaf on one side of the container and the control leaf on the other side. In the central open area of the container, 30 last-instar S. littoralis larvae were placed without making contact to the leaves. The number of larvae were scored on each castor bean leaf after 1 day of treatment. Data are expressed as means±SE per compound based on a minimum of 2 replicates consisting of 2 groups of 30 larvae each. Fifty percent of larvae on the control and the treated leaf represent a homogeneous distribution over the two leaves (which was the case in the control treatments); 0% larvae on the treated leaf indicates a complete insect repellent action. An illustration is give in the next two photographs which were taken after a few hours (photo 1) and after 1 day (photo 2).

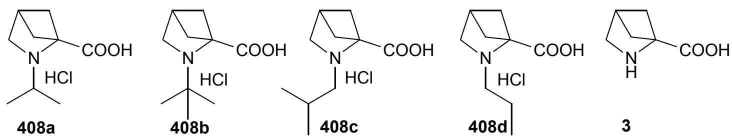
Photo 1: Photo of the bioassays. On the right is the control leaf, treated only with solvent; On the left is the leaf treated with the methanoproline analogue **414a** (after 2 hours).

Photo 2: Photo of the bioassays. On the right is the control leaf, treated only with solvent; On the left is the leaf treated with the methanoproline analogue **414a** (after 1 day).

The data on 2,4-methanoproline and the N-alkyl 2,4-methanoproline derivatives **408** are presented in Graph 1.

Graph 1: Distribution of the larvae on control and treated leaf (4 ml of a 0.1% solution in distilled water)

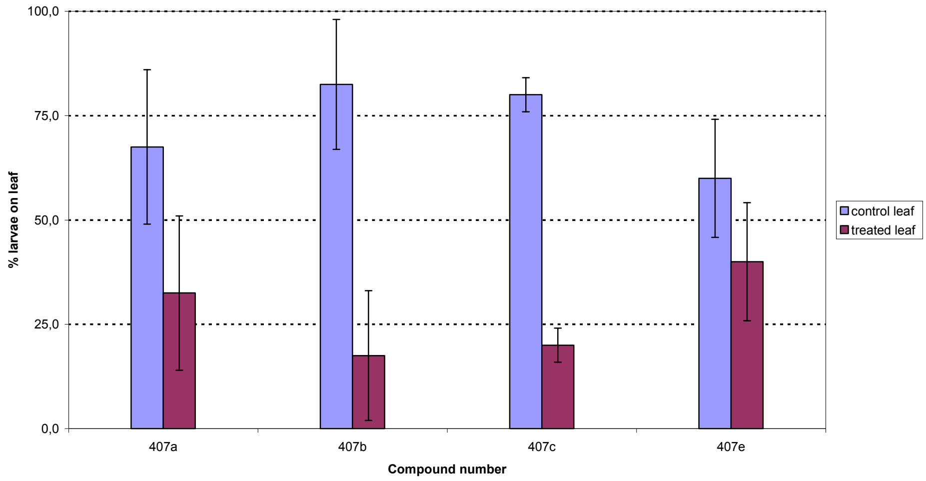


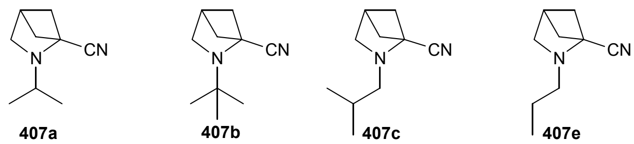


From the data presented in Graph 1, it is noteworthy to see that 2,4-methanoproline **3** did not show any considerable anti-feedant activity, although this has been suggested several times in literature. The activity was tested only on *Spodoptera littoralis* as a test insect, therefore it cannot be stated that 2,4-methanoproline has no anti-feedant activity at all, but it is remarkable that no activity could be detected for this compound. On the other hand, a significant repellent activity was observed for the N-propyl derivative **408d**.

The next series of tests were performed on the anino nitriles **407**. The results are depicted in Graph 2.

Graph 2: Distribution of the larvae on control and treated leaf
(4 ml of a 0.1% solution in acetone)

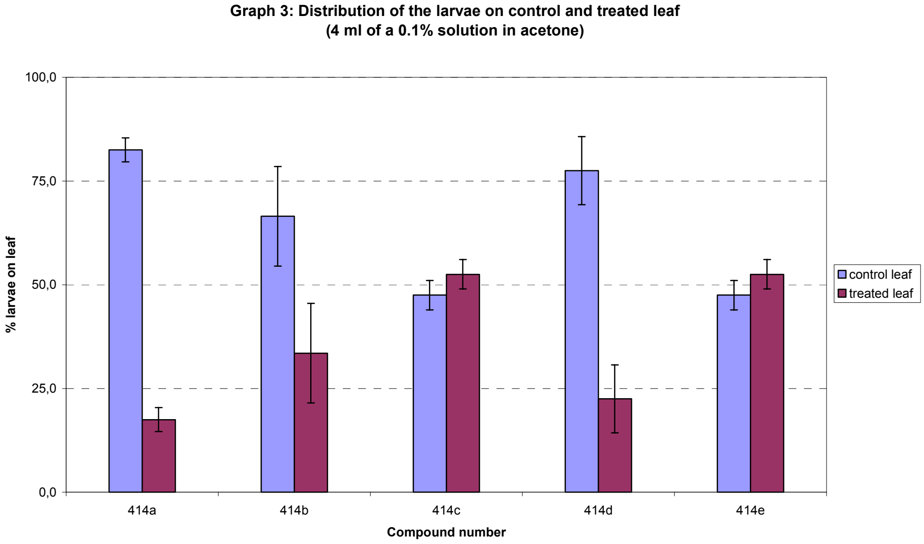


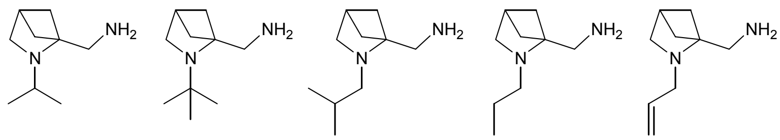


407a **407b** **407c** **407e**

From these results, it follows that not all the amino nitrile derivatives possess an anti-feedant activity. The N-isobutyl **407c** and N-t-butyl **407b** derivatives show significant activity but the N-isopropyl **407a** and N-propyl **407e** derivatives are inactive towards the tested larvae.

In the last series of tests the amines **414** were tested and again big differences in activity were found depending on the N-alkyl substituent group: the N-isopropyl derivative **414a** especially showed a potent activity.



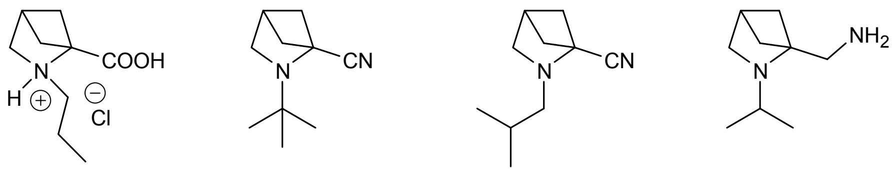


414a **414b** **414c** **414d** **414e**

Although 2,4-methanoproline showed no activity, much to our surprise, it was observed that four other compounds showed a considerable anti-feedant activity. The compounds **408d**, **407b**, **407c** and **414a** gave a result of 80% preference for the untreated leaves in the experiment described.

These results are not obvious to interpret in terms of the Structure-Activity Relation since activity was detected for a different functional group (CN, COOH and CH_2NH_2) and for different alkyl substituents (R = propyl, isobutyl, t-butyl and isopropyl).

Active methanoproline derivatives



408d **407b** **407c** **414a**

Further, the 2-azabicylo[2.1.1]hexane is presumably not the only structural moiety required to induce activity, otherwise all the tested compounds should show some activity. Therefore, a synergistic effect between the skeleton, the functional group and the side chain needs to be important to produce the activity. Further experiments with other pest insects will have to be performed in order to get a good view on the anti-feedant potency of the 2-azabicyclohexanes. The tricyclic derivatives **447**, **451** and **470** were not yet tested in similar experiments.

6. Experimental part

6.1. Instrumental material

6.1.1. Flash chromatography

The purification of reaction mixtures was performed through flash chromatography using a glass column with silica gel (Across, particle size 0.035-0.070 mm, Pore diameter ca. 6 nm).[202] Solvent systems were determined via initial TLC analysis (Merck Kieselgel $60F_{254}$, precoated 0.25 mm). As detection methods UV light, adsorption with iodide vapours or colouring with $KMnO_4$-KOH were used.

6.1.2. NMR-spectroscopy

High resolution ^{1}H-NMR (270 MHz), ^{13}C-NMR (68 MHz) and ^{31}P (109.4 MHz) spectra were run with Jeol JNM-EX 270 NMR spectrometer or on a Jeol JNM-EX 300 NMR. Peak assignments were obtained with the aid of DEPT, 2D-HETCOR, 2D-COSY spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. Tetramethylsilane (TMS) was used as internal standard when organic solvents were used and acetonitrile ($C\underline{H}_3CN$, 2.0 ppm in ^{1}H-spectra) when compounds were dissolved in D_2O.

6.1.3. Mass spectrometry

Mass spectra were recorded on a Varian MAT 112 spectrometer (70eV), using either GC-MS) coupling or a direct inlet system. Some volatile samples were recorded on an HP 6890 GC coupled with a HP 5973 MSD (Mass selective detector; quadrupole). Mass spectra of molecules with a high molecular weight were recorded on an Agilent 1100 Series VS (ES, 4000V) mass spectrometer.

6.1.4. Infrared spectra

IR-spectra were obtained from a Perkin Elmer 983G, or a Perkin Elmer Spectrum One infrared spectrometer. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained.

6.1.5. Gas chromatography

The purity of the synthesised compounds or reaction mixtures was analysed by gas chromatography, using a Delsi DI 200 (fused silica, AT-1, film thickness 0.25 μm, length 30 m, i.d. 0.25 mm, N_2 as carrier gas, FID, H_2 gas)

6.1.6. HPLC

High Performance Liquid Chromatography (HPLC) was carried out using a Kontron instrument equipped with two Kontron 420 pumps and a Kontron 430 UV detector.

6.1.7. Dry solvents

Diethyl ether and tetrahydrofuran were distilled from sodium and sodium benzophenone ketyl, whereas dichloromethane was distilled from calcium hydride prior to use. Toluene and benzene were dried over sodium and distilled, while DMSO was distilled and kept over molecular sieves. Methanol was dried with magnesiummethoxide and distilled.

6.1.8. Melting point

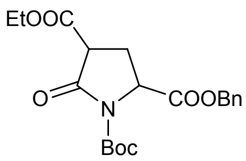
Melting points of crystalline compounds were measured with a Buchi 540 apparatus and are uncorrected.

6.2. Entry from pyroglutamate derivatives

6.2.1. Alkylation on the pyroglutamate ring

2-Benzyl 1-t-butyl 4-ethyl-5-oxo-1,2,4-pyrrolidinetricarboxylate 217c

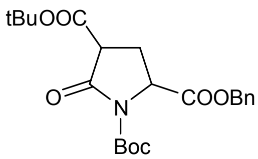
2.5 g of 2-benzyl 1-t-butyl-5-oxo-1,2-pyrrolidinedicarboxylate was dissolved in 30 ml of dry THF and cooled in an acetone bath to -78°C. At this temperature and under a nitrogen atmosphere, 15.6 ml (2 equiv.) of a 1M LiHMDS solution was added while stirring was continued at this temperature. After 2 hours 2.55 g of ethyl chloroformate was added (dissolved in 10 ml of THF) and the temperature maintained at -78°C for 3 hours. The reaction was quenched with 5 ml of saturated NH_4Cl/NH_4OH solution and 40 ml of water was added. The mixture was extracted with diethyl ether and dried with $MgSO_4$. After filtration and evaporation of the solvent the crude product was purified by means of chromatography. 2.2 g of 2-benzyl 1-t-butyl 4-ethyl-5-oxo-1,2,4-pyrrolidinetricarboxylate was obtained as a clear oil (yield = 72 %; 69/31).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.31 (3H, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 1.44 (9H, s, t-Bu), 2.23 (1H, ddd, *J*= 13.4 Hz, *J*= 9.0 Hz, *J*= 2.3 Hz, $C\underline{H}_aH_b$ ring), 2.74 (1H, ddd, *J*= 13.4 Hz, *J*= 10.0 Hz, *J*= 10.1 Hz, $CH_a\underline{H}_b$ ring), 3.65 (1H, dd, *J*= 10.4 Hz, *J*= 9.1 Hz, CH 4), 4.15-4.30 (2H, m, $COOC\underline{H}_2CH_3$), 4.72 (1H, dd, *J*= 9.6 Hz, *J*= 2.3 Hz, NCH 2), 5.16-5.28 (5H, s, $COOC\underline{H}_2Ph$), 7.37 (5H, s, CH, Ph); MINOR: 1.27 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 1.42 (9H, s, t-Bu), 2.53-2.61 (2H, m, CH_2 ring), 3.53 (1H, dd, *J*= 9.1 Hz, *J*= 5.4 Hz, CH 4), 4.09-4.20 (2H, m, $COOC\underline{H}_2CH_3$), 4.66 (1H, dd, *J*= 8.6 Hz, *J*= 4.9 Hz, NCH 2), 5.13-5.20 (2H, m, $COOC\underline{H}_2Ph$), 7.37 (5H, s, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 14.07 ($COOCH_2\underline{C}H_3$), 25.34 (CH_2 ring), 27.73 (t-Bu), 48.50 (CH, C4), 57.25 (NCH, C2), 62.07 ($COO\underline{C}H_2CH_3$), 67.51 ($\underline{C}H_2Ph$), 84.11 ($C_{quat.}$, t-Bu), 128.52 (CH), 128.61 (CH), 128.70 (CH), 134.95 ($C_{quat.}$, Ph), 148.95 (C=O, Boc), 168.01 (C=O), 170.74 (C=O); MINOR: 14.20 ($COOCH_2\underline{C}H_3$), 24.73 (CH_2 ring), 27.73 (t-Bu), 48.82 (CH, C4), 57.68 (NCH, C2), 62.17 ($COO\underline{C}H_2CH_3$), 67.40 ($COO\underline{C}H_2Ph$), 83.93 ($C_{quat.}$, t-Bu), 128.52 (CH), 128.61 (CH), 128.70 (CH), 135.11 ($C_{quat.}$, Ph), 149.00 (C=O, Boc), 167.36 (C=O), 167.71 (C=O), 170.26 (C=O). **IR (cm^{-1}) ν_{max} :** 1797, 1733. **MS: m/z (%):** (direct inlet) no M^+, 137 (28), 136 (26), 86 (76), 84 (100), 51 (39), 49 (99). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.09. (yield= 72 %).

2-Benzyl 1,4-di-t-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate 217d

The workup of the reaction is the same as described for the synthesis of 2-benzyl 1-t-butyl 4-ethyl 5-oxo-1,2,4-pyrrolidinetricarboxylate. Only 1.5 equiv. of di-t-butyldicarbonate was used as electrophile and once it was added the reaction was allowed to warm to room temperature. The product crystallises as a white powder (yield = 77 %; 78/32).



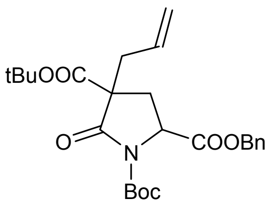
^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR, *MINOR*, not assigned: 1.40 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 1.45 (9H, s, t-Bu), 1.47 (9H, s, t-Bu), 2.18 (1H, ddd, *J*= 13.4 Hz, *J*= 9.0 Hz, *J*= 2.3 Hz, CH_aH_b), *2.47-2.53* (2H, m, CH_2 ring), 2.67 (1H, ddd, *J*= 13.5 Hz, *J*= 10.1 Hz, *J*= 9.9 Hz, CH_aH_b), *3.42* (1H, dd, *J*= 6.4 Hz, *J*= 8.4 Hz, CH), 3.53 (1H, dd, *J*= 10.4 Hz, *J*= 9.1 Hz, CH), *4.61* (1H, dd, *J*= 5.9 Hz, *J*= 7.9 Hz, NCH), 4.68 (1H, dd, *J*= 9.6 Hz, *J*= 2.3 Hz, NCH), 5.13-5.28 (2H, m, $COOCH_2Ph$), 7.26-7.45 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR, *MINOR*, not assigned: *24.71* (CH_2 ring), 25.23 (CH_2 ring), 27.67 (t-Bu), *27.76* (t-Bu), 27.85 (t-Bu), *28.23* (t-Bu), 49.29 (CH, C4), *49.67* (CH, C4), 57.18 (NCH), *57.56* (NCH), *67.24* ($COOCH_2Ph$), 67.38 ($COOCH_2Ph$), 82.59 ($C_{quat.}$, t-Bu), 83.63 ($C_{quat.}$, t-Bu), 83.84 ($C_{quat.}$, t-Bu), 128.44 (CH), 128.50 (CH), 128.55 (CH), 128.66 (CH), 135.02 ($C_{quat.}$, Ph), *135.16* ($C_{quat.}$, t-Bu), 148.93 (C=O, Boc), *148.98* (C=O, Boc), 156.6 (C=O), 166.45 (C=O), 167.09 (C=O), 168.14 (C=O), 168.43 (C=O), 170.42 (C=O), 170.83 (C=O). **IR (cm^{-1}) ν_{max} :** 1703, 1726. **MS: m/z (%):** (direct inlet) no M^+, 308 (7), 264 (25), 129 (19), 128 (98), 110 (37), 91 (87), 57 (100). **Chromatography**: Hex/EtOAc 70/30 R_f= 0.31 **Mp**.= 84-86.5°C. (yield = 77 %).

6.2.1.1. Alkylation of 2-benzyl 1,4-di-t-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate at the 4-position

In a classical experiment, 1 g of 2-benzyl 1,4-di-t-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (2.3 mmol) was dissolved in 10 ml of dry THF and kept under a positive N_2-pressure. 0.29 g of KOtBu (1.1 equiv.) was added and the mixture was stirred for 30 minutes when the electrophile (2 equiv.) was added. The reaction mixture was subsequently refluxed overnight. After cooling, the solution was poured in water and extracted with diethyl ether. The organic layers were combined and dried with $MgSO_4$. Filtering off the drying agent and evaporating the solvent led to a mixture which was purified by chromatography to remove the excess of electrophile.

2-Benzyl 1,4-di-t-butyl 4-allyl-5-oxo-1,2,4-pyrrolidinetricarboxylate 227a

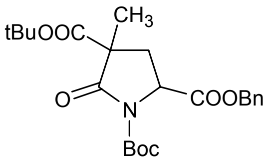
The reaction was performed on 2.3 mmol of starting material. Allyl bromide was used as electrophile (yield = 81 %; 51/49). The product was obtained as a clear viscous oil.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR, *MINOR*, not assigned: *1.41* (9H, s, t-Bu), 1.41 (9H, s, t-Bu), *1.44* (9H, s, t-Bu), 1.45 (9H, s, t-Bu), 1.92 (1H, dd, *J*= 13.7 Hz, *J*= 7.1 Hz, CH_aH_b ring), *2.25* (1H, dd, *J*= 13.7 Hz, *J*= 10.1 Hz, CH_aH_b ring), 2.47 (2H, dd, *J*= 14.0 Hz, *J*= 7.1 Hz, $CH_aH_bCH=CH_2$), 2.64-2.80 (2H, m, CH_aH_b ring, $CH_aH_bCH=CH_2$), *4.57* (1H, dd, *J*= 10.1 Hz, *J*= 2.5 Hz, NCH, C2), 4.64 (1H, dd, *J*= 9.1 Hz, *J*= 7.1 Hz, NCH, C2), 4.96-5.28 (4H, m, CH_2Ph + $CH_2CH=CH_2$), 5.56-5.72 (1H, m, $CH_2CH=CH_2$), 7.36 (5H, s, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR, *MINOR*, not assigned: 27.64 (t-Bu), 29.40 (CH_2 ring), *29.90* (CH_2 ring), 37.74 ($CH_2CH=CH_2$), *39.87* ($CH_2CH=CH_2$), *56.26* ($C_{quat.}$, C4), 56.75 (NCH ring), 56.82 ($C_{quat.}$, C4), *56.99* (NCH ring), *67.13* (CH_2Ph), 67.21 (CH_2Ph), *82.62* ($C_{quat.}$, t-Bu), *82.77* ($C_{quat.}$, t-Bu), 83.40 ($C_{quat.}$, t-Bu), 83.74 ($C_{quat.}$, t-Bu), 119.85 ($C{=}\underline{C}H_2$), 128.37 (CH), 128.52 (CH), 128.61 (CH), *131.88* ($\underline{C}H{=}CH_2$), 132.34 ($\underline{C}H{=}CH_2$), 134.98 ($C_{quat.}$, Ph), *135.22* ($C_{quat.}$, Ph), 148.96 (C=O, Boc), 167.81 (C=O), 168.46 (C=O), 170.01 (C=O), 170.19 (C=O), 170.51 (C=O), 170.85 (C=O). **IR (cm^{-1}) ν_{max} :** 1721 (br.), 1792. **MS: m/z (%):** (direct inlet) no M^+, 347 (40), 302 (100), 167 (96), 149 (69), 91 (88), 84 (80), 57 (67).

2-Benzyl 1,4-di-t-butyl 4-methyl-5-oxo-1,2,4-pyrrolidinetricarboxylate 227b

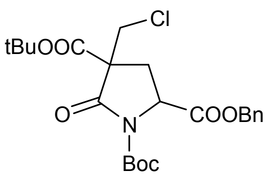
The reaction was performed on 2.3 mmol of starting material. Methyl iodide was used as electrophile (yield = 53 %; 70/30). The product was obtained as a white powder.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.41 (3H, s, CH_3), 1.44 (18H, s, 2 x t-Bu), 1.80 (1H, dd, *J*= 13.4 Hz, *J*= 6.9 Hz, $C\underline{H}_aH_b$ ring), 2.76 (1H, dd, *J*= 13.4 Hz, *J*= 8.9 Hz, $CH_a\underline{H}_b$ ring), 4.65 (1H, dd, *J*= 8.9 Hz, *J*= 6.9 Hz, NCH, C2), 5.16 (1H, d, *J*= 11.9 Hz, $C\underline{H}_aH_bPh$), 5.24 (1H, d, *J*= 11.9 Hz, $CH_a\underline{H}_bPh$), 7.36 (5H, s, CH, Ph); MINOR: 1.39 (3H, s, CH_3), 1.42 (18H, s, 2 x t-Bu), 2.11-2.19 (2H, m, CH_2 ring), 4.60 (1H, dd, *J*= 9.9 Hz, *J*= 3.0 Hz, NCH, C2), 5.13 (1H, d, *J*= 12.2 Hz, $C\underline{H}_aH_bPh$), 5.22-5.29 (1H, m, $CH_a\underline{H}_bPh$), 7.36 (5H, s, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 0 (TMS) MAJOR: 20.25 (CH_3), 27.76 (2 x t-Bu), 33.78 (CH_2 ring), 53.37 ($C_{quat.}$, C4), 56.87 (NCH, C2), 67.44 ($COO\underline{C}H_2Ph$), 82.78 ($C_{quat.}$, t-Bu), 83.95 ($C_{quat.}$, t-Bu), 128.44 (CH), 128.62 (CH), 128.70 (CH), 134.89 ($C_{quat.}$, Ph), 149.27 (C=O, Boc), 169.70 (C=O), 170.99 (C=O), 171.84 (C=O); MINOR: 21.90 (CH_3), 27.67 (2 x t-Bu), 33.41 (CH_2 ring), 53.10 ($C_{quat.}$, C4), 56.12 (NCH, C2), 67.31 ($COO\underline{C}H_2CH_3$), 82.71 ($C_{quat.}$, t-Bu), 83.72 ($C_{quat.}$, t-Bu), 128.50 (CH), 128.62 (CH), 128.70 (CH), 133.13 ($C_{quat.}$, Ph), 149.27 (C=O, Boc), 169.32 (C=O), 170.00 (C=O). **IR (cm^{-1}) ν_{max} :** 1783, 1739. **MS: m/z (%):** (ES, pos) no M^+, 278 (72), 91 (100). Crystallisation in Hex/Et_2O. **Mp.=** 90.4-91.8°C.

2-Benzyl 1,4-di-t-butyl 4-(chloromethyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate 227c

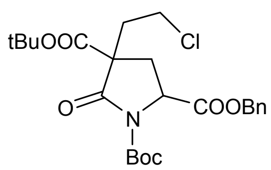
The reaction was performed on 2.3 mmol of starting material. Chloroiodomethane was used as electrophile (yield = 58 %; 53/47). The product was obtained as a white powder.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.41 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 2.54 (1H, dd, *J*= 13.9 Hz, *J*= 10.2 Hz, $C\underline{H}_aH_b$ ring), 2.81 (1H, dd, *J*= 13.9 Hz, *J*= 2.6 Hz, $CH_a\underline{H}_b$ ring), 3.83 (1H, d, *J*= 11.2 Hz, $C\underline{H}_aH_bCl$), 3.96 (1H, d, *J*= 11.2 Hz, $CH_a\underline{H}_bCl$), 4.69 (1H, dd, *J*= 10.2 Hz, *J*= 2.6 Hz, CH ring), 5.15 (1H, d, *J*= 12.2 Hz, $C\underline{H}_aH_bPh$), 5.26 (1H, d, *J*= 12.2 Hz, $CH_a\underline{H}_bPh$), 7.35-7.38 (5H, m, CH, Ph). MINOR: 1.43 (9H, s, t-Bu), 1.47 (9H, s, t-Bu), 2.22 (1H, dd, *J*= 13.3 Hz, *J*= 6.9 Hz, $C\underline{H}_aH_b$ ring), 2.87 (1H, dd, *J*= 13.9 Hz, *J*= 8.9 Hz, $CH_a\underline{H}_b$ ring), 3.80 (1H, d, *J*= 11.3 Hz, $C\underline{H}_aH_bCl$), 3.99 (1H, d, *J*= 11.3 Hz, $CH_a\underline{H}_bCl$), 4.69 (1H, dd, *J*= 9.0 Hz, *J*= 6.9 Hz, CH ring), 5.21 (1H, d, *J*= 12.5 Hz, $C\underline{H}_aH_bPh$), 5.23 (1H, d, *J*= 12.5 Hz, $CH_a\underline{H}_bPh$), 7.35-7.38 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR, *MINOR*, not assigned: *27.64* (t-Bu), 27.73 (t-Bu), 28.77 (CH_2 ring), *29.29* (CH_2 ring), *45.30* (CH_2Cl), 47.08 (CH_2Cl), *56.39* (CH, ring), 56.78 (CH, ring), *59.19* ($C_{quat.}$, C4), 59.55 ($C_{quat.}$, C4), *67.46* (CH_2Ph), 67.55 (CH_2Ph), 84.06 ($C_{quat.}$, t-Bu), 84.15 ($C_{quat.}$, t-Bu), 84.47 ($C_{quat.}$, t-Bu), 128.50 (CH), 128.53 (CH), 128.61 (CH), 128.71 (CH), <u>134.82</u> ($C_{quat.}$, Ph), *135.09* ($C_{quat.}$, Ph), 148.80 (C=O, Boc), 165.87 (C=O), 166.50 (C=O), 167.92 (C=O), 169.93 (C=O), 170.71 (C=O). **IR (cm^{-1}) ν_{max} :** (KBr) 1782, 1742. **MS: m/z (%):** (ES, Pos) no M^+, 314 (12), 312 (28), 91 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.22 and 0.19. **Mp**.: 89.2-90.3°C.

2-Benzyl 1,4-di-t-butyl 4-(2-chloroethyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate 227d

The reaction was performed on 2.3 mmol of starting material. Bromochloroethane was used as electrophile (yield = 26 %). The product was obtained as an oil.

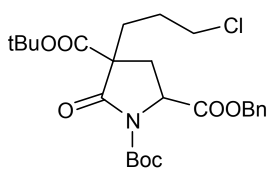


MAJOR: **^{1}H-NMR (300 MHz, $CDCl_3$) δ:** 1.41 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 1.94 (1H, dd, *J*= 13.6 Hz, *J*= 7.3 Hz, $C\underline{H}_aH_b$ ring), 2.15 (1H, ddd, *J*= 14.6 Hz, *J*= 8.9 Hz, *J*= 6.1 Hz, $C\underline{H}_aH_bCH_2Cl$), 2.46 (1H, ddd, *J*= 14.6 Hz, *J*= 8.9 Hz, *J*= 5.8 Hz, $CH_a\underline{H}_bCH_2Cl$), 2.78 (1H, dd, *J*= 13.6 Hz, *J*= 8.7 Hz, $CH_a\underline{H}_b$ ring), 3.38-3.54 (1H, m, $C\underline{H}_aH_bCl$), 3.56-3.66 (1H, m, $CH_a\underline{H}_bCl$), 4.62 (1H, dd, *J*= 8.7 Hz, *J*= 7.3 Hz, CH ring), 5.15 (1H, d, *J*= 12.5 Hz, $C\underline{H}_aH_bPh$), 5.21 (1H, d, *J*= 12.5 Hz, $CH_a\underline{H}_bPh$), 7.33-7.34 (5H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.69 (t-Bu), 27.76 (t-Bu), 31.16 (CH_2 ring), 36.60 ($\underline{C}H_2CH_2Cl$), 39.87 (CH_2Cl), 56.73 ($C_{quat.}$, C4), 57.05 (CH, C2), 67.60 ($COO\underline{C}H_2Ph$), 83.65 ($C_{quat.}$, t-Bu), 84.29 ($C_{quat.}$, t-Bu), 128.70 (CH), 128.73 (CH), 128.79 (CH), 134.80 ($C_{quat.}$, Ph), 149.02 (C=O, Boc), 168.16 (C=O), 170.06 (C=O), 170.78 (C=O). **IR (cm^{-1}) ν_{max} :** 1794, 1729. **MS: m/z (%):** (ES, Pos) no M^+, 328 (16), 326 (50), 190 (20), 91 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.28. **Mp**.= 78-79°C.

MINOR: **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 1.41 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 2.12 (1H, ddd, *J*= 14.5 Hz, *J*= 8.5 Hz, *J*= 6.3 Hz, $C\underline{H}_aH_bCH_2Cl$), 2.30 (1H, dd, *J*= 13.7 Hz, *J*= 9.9 Hz, $C\underline{H}_aH_b$ ring), 2.58 (1H, ddd, *J*= 14.5 Hz, *J*= 8.7 Hz, *J*= 5.6 Hz, $CH_a\underline{H}_bCH_2Cl$), 2.88 (1H, dd, *J*= 13.8 Hz, *J*= 1.9 Hz, $CH_a\underline{H}_b$ ring), 3.49 (1H, ddd, *J*= 11.0 Hz, *J*= 8.5 Hz, *J*= 6.3 Hz, $CH_2C\underline{H}_aH_bCl$), 3.63 (1H, ddd, *J*= 11.1 Hz, *J*= 8.7 Hz, *J*= 5.6 Hz, $CH_2CH_a\underline{H}_bCl$), 4.63 (1H, dd, *J*= 9.9 Hz, *J*= 1.7 Hz, CH ring), 5.14 (1H, d, *J*= 12.2 Hz, $C\underline{H}_aH_bPh$), 5.23 (1H, d, *J*= 12.2 Hz, $CH_a\underline{H}_bPh$), 7.36 (5H, s, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.67 (t-Bu), 27.74 (t-Bu), 31.37 (CH_2 ring), 38.38 ($\underline{C}H_2CH_2Cl$), 39.84 ($CH_2\underline{C}H_2Cl$), 56.33 (CH ring), 56.50 ($C_{quat.}$, C4), 67.44 ($COOCH_2Ph$), 83.72 ($C_{quat.}$, t-Bu), 83.92 ($C_{quat.}$, t-Bu), 128.48 (CH), 128.53 (CH), 128.61 (CH), 135.11 ($C_{quat.}$, Ph), 149.00 (C=O, Boc), 167.40 (C=O), 169.68 (C=O), 169.99 (C=O). **IR (cm^{-1}) ν_{max} :** 1794, 1728. (ES, Pos) no M^+, 328 (10), 326 (30), 91 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.19.

2-Benzyl 1,4-di-t-butyl 4-(3-chloropropyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate 227e

The reaction was performed on 2.3 mmol of starting material. 3-Bromo-1-chloro-propane was used as electrophile (yield = 82 %). The product was obtained as a white powder.



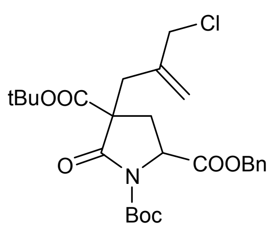
MAJOR: **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 1.44 (9H, s t-Bu), 1.45 (9H, s, t-Bu), 1.37-1.5 (2H, m, $C\underline{H}_2CH_2CH_2Cl$), 1.79-1.88 (2H, m, $CH_2C\underline{H}_aH_bCH_2Cl$ + $C\underline{H}_aH_b$ ring), 2.05-2.14 (1H, m, $CH_2CH_a\underline{H}_bCH_2Cl$), 2.76 (1H, dd, *J*= 13.5 Hz, *J*= 8.9 Hz, $CH_a\underline{H}_b$ ring), 3.46 (2H, t, *J*= 5.9 Hz, CH_2Cl), 4.64 (1H, dd, *J*= 8.9 Hz, *J*= 7.3 Hz, CH ring), 5.19 (1H, d, *J*= 12.0 Hz, $C\underline{H}_aH_bPh$), 5.22

(1H, d, *J*= 12.0 Hz, $CH_a\underline{H}_bPh$), 7.37 (5H, s, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.60 ($CH_2CH_2CH_2$), 27.78 (t-Bu), 30.67 ($CH_2CH_2CH_2$), 31.18 (CH_2 ring), 44.64 (CH_2Cl), 56.85 (CH, C2), 56.99 ($C_{quat.}$, C4), 67.51 (CH_2Ph), 83.22 ($C_{quat.}$, t-Bu), 84.15 ($C_{quat.}$, t-Bu), 128.71 (CH), 128.77 (CH), 134.86 ($C_{quat.}$, Ph), 149.09 (C=O, Boc), 168.68 (C=O), 170.58 (C=O), 170.92 (C=O). **IR (cm^{-1}) ν_{max} :** 1793, 1724. **MS: m/z (%):** (ES, Pos) no M^+, 342 (17), 340 (50), 91 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.27. **Mp**.= 79.2-83.1°C.

MINOR: **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 1.36-1.50 (1H, m, $C\underline{H}_aH_bCH_2CH_2Cl$), 1.41 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 1.64-1.87 (2H, m, $CH_a\underline{H}_bCH_2CH_2Cl$ + $CH_2C\underline{H}_aH_bCH_2Cl$), 2.13-2.25 (1H, m, $CH_2CH_a\underline{H}_bCH_2Cl$), 2.17 (1H, dd, *J*= 13.5 Hz, *J*= 9.9 Hz, $C\underline{H}_aH_b$ ring), 2.82 (1H, dd, *J*= 13.5 Hz, *J*= 2.0 Hz, $CH_a\underline{H}_b$ ring), 3.52 (2H, t, *J*= 5.8 Hz, CH_2Cl), 4.61 (1H, dd, *J*= 9.9 Hz, *J*= 2.0 Hz, CH ring), 5.12 (1H, d, *J*= 12.0 Hz, $C\underline{H}_aH_bPh$), 5.24 (1H, d, *J*= 12.0 Hz, $CH_a\underline{H}_bPh$), 7.34-7.38 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.69 (t-Bu), 27.74 (t-Bu), 27.92 ($CH_2CH_2CH_2$), 30.98 (CH_2 ring), 33.24 ($CH_2CH_2CH_2$), 44.47 (CH_2Cl), 56.24 (CH, C2), 56.73 ($C_{quat.}$, C4), 67.42 (CH_2Ph), 83.16 ($C_{quat.}$, t-Bu), 83.83 ($C_{quat.}$, t-Bu), 128.48 (CH), 128.54 (CH), 128.61 (CH), 135.09 ($C_{quat.}$, Ph), 149.09 (C=O, Boc), 167.94 (C=O), 170.19 (C=O), 170.22 (C=O). **IR (cm^{-1}) ν_{max} :** 1792, 1725. **MS: m/z (%):** (ES, Pos) no M^+, 342 (15), 340 (45), 91 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.19. **Mp**.= 91.5-93.0°C.

2-Benzyl 1,4-di-t-butyl 4-[2-(chloromethyl)-2-propenyl]-5-oxo-1,2,4-pyrrolidine-tricarboxylate 227f

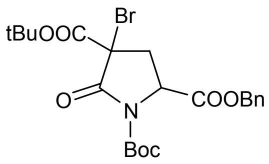
The reaction was performed on 2.3 mmol of starting material. 3-Chloro-2-(chloromethyl)-1-propene was used as electrophile (yield = 60 %; 64/36). The product was obtained as an oil.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.41 (9H, s, t-Bu), 1.43 (9H, s, t-Bu), 2.32 (1H, dd, *J*= 13.6 Hz, *J*= 10.2 Hz, $C\underline{H}_aH_b$ ring), 2.52 (1H, d, *J*= 15.5 Hz, $C\underline{H}_aH_bC{=}CH_2$), 2.93 (1H, dd, *J*= 13.6 Hz, *J*= 2 Hz, $CH_a\underline{H}_b$ ring), 3.09 (1H, d, *J*= 15.5 Hz, $CH_a\underline{H}_bC{=}CH_2$), 3.92 (2H, s, CH_2Cl), 4.61 (1H, dd, *J*= 10.2 Hz, *J*= 2 Hz, CH ring), 5.01 (1H, br. s, $C{=}C\underline{H}_aH_b$), 5.13 (1H, d, *J*= 12.2 Hz, $C\underline{H}_aH_bPh$), 5.19 (1H, br. s, $C{=}CH_a\underline{H}_b$), 5.24 (1H, d, *J*= 12.5 Hz, $CH_a\underline{H}_bPh$), 7.36 (5H, s, Ph). MINOR: 1.41 (9H, s, t-Bu), 1.44 (9H, s, t-Bu), 1.96 (1H, dd, *J*= 13.8 Hz, *J*= 6.9 Hz, $C\underline{H}_aH_b$ ring), 2.60 (1H, d, *J*= 16.0 Hz, $C\underline{H}_aH_bC{=}CH_2$), 2.88 (1H, dd, *J*= 13.8 Hz, *J*= 8.9 Hz, $CH_a\underline{H}_b$ ring), 3.01 (1H, d, *J*= 16 Hz, $CH_a\underline{H}_bC{=}CH_2$), 3.99 (2H, s, CH_2Cl), 4.64 (1H, dd, *J*= 8.9 Hz, *J*= 6.9 Hz, CH ring), 4.86 (1H, br. s, $C{=}C\underline{H}_aH_b$), 5.20 (1H, d, *J*= 13.2 Hz, $C\underline{H}_aH_bPh$), 5.24 (1H, d, *J*= 13.2 Hz, $CH_a\underline{H}_bPh$), 5.28 (1H, br. s, $C{=}CH_a\underline{H}_b$), 7.36 (5H, s, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 28.21 (t-Bu), 28.32 (t-Bu), 31.61 (CH_2 ring), 39.43 (CH_2), 48.88 (CH_2Cl), 56.91 (CH, C2), 57.22 ($C_{quat.}$, C4), 67.98 (CH_2Ph), 83.88 ($C_{quat.}$, t-Bu), 84.37 ($C_{quat.}$, t-Bu), 119.35 ($C{=}\underline{C}H_2$), 129.04 (CH), 129.15 (CH), 135.72 ($C_{quat.}$, Ph), 140.93 ($\underline{C}{=}CH_2$), 149.60 (C=O, Boc), 168.09 (C=O), 170.49 (C=O), 170.73 (C=O), 171.54 (C=O). MINOR: 28.25 (t-Bu), 28.47 (t-Bu), 30.39 (CH_2 ring), 37.38 (CH_2), 48.99 (CH_2Cl), 57.22 (CH), 57.45 ($C_{quat.}$, C4), 67.98 (CH_2Ph), 83.99 ($C_{quat.}$, t-Bu), 84.71 ($C_{quat.}$, t-Bu), 119.01 ($C{=}\underline{C}H_2$), 129.18 (CH), 129.25 (CH), 135.47 ($C_{quat.}$, Ph), 140.93 ($\underline{C}{=}CH_2$), 149.60 (C=O, Boc), 168.89 (C=O), 170.73 (C=O), 170.93 (C=O), 171.54 (C=O). **IR (cm^{-1}) ν_{max} :** 1795, 1725. **MS: m/z (%):** (ES, Pos) no M^+, 354 (30), 352 (85), 91 (100).

2-Benzyl 1,4-di-t-butyl 4-bromo-5-oxo-1,2,4-pyrrolidinetricarboxylate 227g

The reaction was performed on 2.3 mmol of starting material. NBS was used as electrophile (yield = 29 %; 53/47). The general procedure was followed, but instead of refluxing the reaction mixture, it was stirred at room temperature overnight. The product was obtained as a yellow oil.

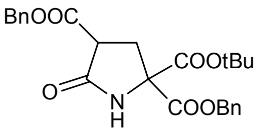


^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.48 (9H, s, t-Bu), 1.50 (9H, s, t-Bu), 2.74 (1H, dd, *J*= 14.2 Hz, *J*= 8.3 Hz, $C\underline{H}_aH_b$ ring), 3.06 (1H, dd, *J*= 14.2 Hz, *J*= 5.9 Hz, $CH_a\underline{H}_b$ ring), 4.65 (1H, dd, *J*= 8.3 Hz, *J*= 5.6 Hz, CH ring), 5.18-5.33 (2H, m, CH_2Ph), 7.36 (5H, s, Ph); MINOR: 1.44 (9H, s, t-Bu), 1.45 (9H, s, t-Bu), 2.69 (1H, dd, *J*= 14.7 Hz, *J*= 2.7 Hz, $C\underline{H}_aH_b$ ring), 3.31 (1H, dd, *J*= 14.7 Hz, *J*= 9.2 Hz, $CH_a\underline{H}_b$ ring), 4.76 (1H, dd, *J*= 9.2 Hz, *J*= 2.7 Hz, CH ring), 5.11-5.20 (2H, m, CH_2Ph), 7.36 (5H, s, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 27.73 (t-Bu), 27.76 (t-Bu), 36.89 (CH_2 ring), 56.51 (CH, C2), 56.91 ($C_{quat.}$, C4), 67.71 ($\underline{C}H_2Ph$), 84.67 ($C_{quat.}$, t-Bu), 85.16 ($C_{quat.}$, t-Bu), 128.66 (CH), 128.70 (CH), 134.79 ($C_{quat.}$, Ph), 149.04 (C=O, Boc), 164.09 (C=O), 165.71 (C=O), 169.34 (C=O), 169.38 (C=O); MINOR: 27.57 (t-Bu), 27.69 (t-Bu), 37.34 (CH_2 ring), 56.21 (CH, C2), 56.68 ($C_{quat.}$, C4), 67.91 (CH_2Ph), 84.81 ($C_{quat.}$, t-Bu), 85.35 ($C_{quat.}$, t-Bu), 128.55 (CH), 128.77 (CH), 134.71 ($C_{quat.}$, Ph), 148.82 (C=O, Boc), 165.55 (C=O), 168.35 (C=O), 169.34 (C=O), 169.38 (C=O). **IR (cm^{-1}) ν_{max} :** 1798, 1733. **MS: m/z (%):** (ES, Pos) no M^+, 344 (28), 342 (32), 91 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.29.

6.2.1.2. Migration of the N-Boc group to the C2- position of the pyroglutamate ring.

2,4-Dibenzyl 2-t-butyl 5-oxo-2,2,4-pyrrolidinetricarboxylate 233

To a solution of 0.74 g (1.63 mmol) benzyl 4-(benzyloxycarbonyl)-1-(t-butoxycarbonyl)-pyroglutamate in 15 ml of dry THF (under a N_2-atmosphere), 4.9 ml (4.9 mmol, 3 equiv.) of LiHMDS (1M in THF) was added at -78°C. After stirring for two hours at this temperature, the reaction was slowly allowed to warm up overnight in the acetone bath. After quenching the reaction with a saturated NH_4Cl/NH_4OH solution 20 ml of diethyl ether was added. After washing the organic layer with water (2 x 15 ml), the water layer was extracted with diethyl ether (3 x 40 ml). The organic phases were combined and dried with $MgSO_4$. After filtration and evaporation of the solvent a viscous oil was obtained. Purification by flash chromatography gave 0.53 g 2,4-dibenzyl 2-t-butyl 5-oxo-2,2,4-pyrrolidinetricarboxylate as a mixture of two isomers (54/46; yield = 72 %; 51/49).

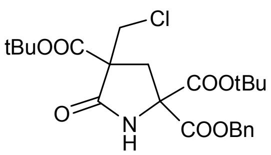


^{1}H-NMR (270 MHz, $CDCl_3$) δ: $\underline{\text{MAJOR}}$, *MINOR*, not assigned: *1.32* (9H, s, t-Bu), $\underline{1.34}$ (9H, s, t-Bu), 2.82-2.94 (2H, m, CH_2), 3.57-3.64 (1H, m, $C\underline{H}CH_2$), 5.13-5.26 (4H, m, $COOC\underline{H}_2Ph$), 6.54 (1H, NH), 7.26-7.37 (10H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** $\underline{\text{MAJOR}}$, *MINOR*, not assigned: *27.51* (t-Bu), $\underline{27.55}$ (t-Bu), $\underline{31.21}$ (CH_2 ring), *31.32* (CH_2 ring), $\underline{47.12}$ (CH, C4), *47.19* (CH, C4), *66.88* ($C_{quat.}$, C2), $\underline{67.21}$ ($C_{quat.}$, C2), *67.49* ($COO\underline{C}H_2Ph$), $\underline{67.53}$ ($COO\underline{C}H_2Ph$), *68.03*

(COO$\underline{C}H_2$Ph), $\underline{68.21}$ (COO$\underline{C}H_2$Ph), $\underline{84.17}$ ($C_{quat.}$, t-Bu), *84.31* ($C_{quat.}$, t-Bu), *128.30* (CH), $\underline{128.34}$ (CH), *128.43* (CH), $\underline{128.55}$ (CH), *128.66* (CH), $\underline{128.69}$ (CH), $\underline{134.55}$ ($C_{quat.}$, Ph), *134.70* ($C_{quat.}$, Ph), *135.27* ($C_{quat.}$, Ph), $\underline{135.33}$ ($C_{quat.}$, Ph), 166.41 (C=O), 166.75 (C=O), 167.98 (C=O), 168.35 (C=O), 170.83 (C=O). **^{1}H-NMR (270 MHz, C_6D_6) δ:** $\underline{1.18}$ (9H, s, t-Bu), *1.21* (9H, s, t-Bu), $\underline{2.62}$ (1H, dd, *J*= 13.9 Hz, *J*= 9.2 Hz, $C\underline{H}_aH_b$), *2.68* (1H, dd, *J*= 13.7 Hz, *J*= 9.6 Hz, $C\underline{H}_aH_b$), *3.04* (1H, dd, *J*= 13.7 Hz, *J*= 10.6 Hz, $CH_a\underline{H}_b$), $\underline{3.06}$ (1H, dd, *J*= 13.9 Hz, *J*= 11.2 Hz, $CH_a\underline{H}_b$), 3.39-3.46 (1H, m, CH), 4.86-4.99 (4H, m, CH_2Ph), 7.04-7.24 (10H, m, CH, Ph), *8.07*(1H, br. s, NH), $\underline{8.10}$ (1H, br. s, NH). **^{13}C-NMR (68 MHz, C_6D_6) δ:** *27.39* (t-Bu), $\underline{27.46}$ (t-Bu), $\underline{31.59}$ (CH_2 ring), *31.46* (CH_2 ring), $\underline{47.69}$ (CH, C4), *47.76* (CH, C4), 67.24 ($\underline{C}H_2$Ph), 67.31 ($\underline{C}H_2$Ph), 67.67 ($\underline{C}H_2$Ph), 67.74 ($\underline{C}H_2$Ph), $\underline{67.82}$ ($C_{quat.}$, C2), *68.00* ($C_{quat.}$, C2), $\underline{83.36}$ ($C_{quat.}$, t-Bu), *83.49* ($C_{quat.}$, t-Bu), 128.21 (CH), 128.25 (CH), 128.39 (CH), 128.66 (CH), 128.75 (CH), 135.56 ($C_{quat.}$, Ph), 135.70 ($C_{quat.}$, Ph), 136.15 ($C_{quat.}$, Ph), 136.21 ($C_{quat.}$, Ph), 167.04 (C=O), 167.36 (C=O), 168.51 (C=O), 168.75 (C=O), 168.78 (C=O), 168.87 (C=O), 171.79 (C=O), 171.86 (C=O). **IR (cm^{-1}) ν_{max} :** 3032, 1610, 1495, 1454, 1741, 1714. **MS: m/z (%):** (ES, Pos) 454 (M^++H, 25), 398 (100), 181 (34), 91 (35). **Chromatography:** Hex/EtOAc 70/30 R_f= 0.19.

2-Benzyl 2,4-di-t-butyl 4-(chloromethyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate 228a

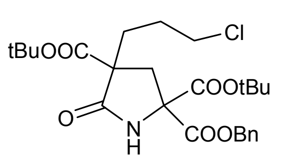
To a solution of 0.1 g (0.2 mmol) of 2-benzyl 1,4-di-t-butyl 4-(chloromethyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate in 2 ml of dry THF at -78°C and under a N_2-atmosphere, 0.32 ml (1.5 equiv.) of a LiHMDS solution (1M in hexanes) was added and stirred for 30 minutes at this temperature. After allowing the reaction to warm up overnight to room temperature it was quenched with a saturated NH_4Cl/NH_4OH solution. The organic phase was washed with water and dried with $MgSO_4$. Filtering off the $MgSO_4$ and evaporating the filtrate gave the crude product that was purified by column chromatography which led to 0.061 g of 2-benzyl 2,4-di-t-butyl 4-(chloromethyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate as a clear oil (yield = 61 %).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.34 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 2.90 (1H, d, *J*= 14.5 Hz, $C\underline{H}_aH_b$ ring), 3.23 (1H, d, *J*= 14.5 Hz, $CH_a\underline{H}_b$ ring), 3.86 (1H, d, *J*= 11.4 Hz, $C\underline{H}_aH_b$Cl), 3.90 (1H, d, *J*= 11.4 Hz, $CH_a\underline{H}_b$Cl), 5.22 (1H, d, *J*= 11.9 Hz, $C\underline{H}_aH_b$Ph), 5.26 (1H, d, *J*= 11.9 Hz, $CH_a\underline{H}_b$Ph), 6.41 (1H, br. s, NHCO), 7.36 (5H, s, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.53 (t-Bu), 27.66 (t-Bu), 34.44 (CH_2 ring), 45.48 (CH_2Cl), 57.68 ($C_{quat.}$, C4), 66.31 ($C_{quat.}$, C2), 68.18 (CH_2Ph), 83.74 ($C_{quat.}$, Ph), 84.46 ($C_{quat.}$, t-Bu), 128.70 (CH), 128.79 (CH), 128.88 (CH), 134.72 ($C_{quat.}$, Ph), 167.33 (C=O), 167.96 (C=O), 170.83 (C=O). **IR (cm^{-1}) ν_{max} :** 1739. **MS: m/z (%):** (ES, Pos) no M^+, 358 (10), 356 (20), 91 (100). **Chromatography**: 80/20 Hex/EtOAc R_f= 0.30.

2-Benzyl 2,4-di-t-butyl 4-(3-chloropropyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate 228b

The same procedure as for the synthesis of 2-benzyl 2,4-di-t-butyl 4-(chloromethyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate was applied (yield = 64 %). The product was obtained as a clear oil.

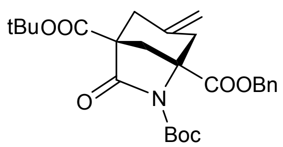


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.33 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 1.39-1.47 (2H, m, C$\underline{H}_2$$CH_2CH_2Cl$), 1.78-1.87 (1H, m, $CH_2C\underline{H}_aH_bCH_2Cl$), 2.05-2.12 (1H, m, $CH_2CH_a\underline{H}_bCH_2Cl$), 2.53 (1H, d, *J*= 14.3 Hz, $C\underline{H}_aH_b$ ring), 3.16 (1H, d, *J*= 14.3 Hz, $CH_a\underline{H}_b$ ring), 3.53-3.55 (2H, m, CH_2Cl), 5.22 (2H, br. s, CH_2Ph), 6.39 (1H, br. s, N$\underline{H}$C=O), 7.36 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.61 (t-Bu), 27.78 (t-Bu), 27.78 ($\underline{C}H_2CH_2CH_2Cl$), 31.75 ($CH_2\underline{C}H_2CH_2Cl$), 36.39 ($CH_2$ ring), 44.80 (CH_2Cl), 55.20 ($C_{quat.}$, C4), 66.39 ($C_{quat.}$, C2), 68.11 ($COOCH_2Ph$), 82.79 ($C_{quat.}$, t-Bu), 84.44 ($C_{quat.}$, t-Bu), 128.77 (CH), 129.22 (CH), 134.86 ($C_{quat.}$, Ph), 166.97 (C=O), 168.35 (C=O), 169.36 (C=O), 173.70 (C=O). **IR (cm^{-1}) ν_{max} :** 1742, 2978. **MS: m/z (%):** (ES, Pos) no M^+, 386 (20), 384 (57), 91 (100). **Chromatography**: Hex/EtOAc 70/30 R_f= 0.21.

6.2.1.3. Synthesis of the 7-oxo-6-azabicyclo[3.2.1]octane skeleton

5-Benzyl 1,6-di-t-butyl 3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-1,5,6-tricarboxylate 232

0.28 g of 2-benzyl 1,4-di-t-butyl 4-[2-(chloromethyl)-2-propenyl]-5-oxo-1,2,4-pyrrolidinetricarboxylate was dissolved in 4 ml of dry THF and kept under a positive N_2 pressure during the reaction. The mixture was cooled to -78°C and 0.66 ml of LiHMDS (1.2 equiv.; 1M solution in hexanes) was added and the solution was slowly allowed to warm up to room temperature overnight keeping the flask in the acetone bath. After quenching the reaction with a NH_4Cl/NH_4OH solution, an extra amount of 10 ml of water was added and the reaction mixture was extracted with diethyl ether (3 x 40 ml). The organic phases were combined and dried with $MgSO_4$. Filtering off the $MgSO_4$ and evaporating the solvent gave the crude product as an oil and was further purified by column chromatography. 0.21 g of 5-benzyl 1,6-di-t-butyl 3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-1,5,6-tricarboxylate was obtained as an oil (yield = 81 %).

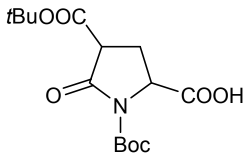


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.42 (9H, s, t-Bu), 1.48 (9H, s, t-Bu), 1.96 (1H, d, *J*= 11.2 Hz, $C\underline{H}_aH_b$), 2.45 (1H, d, *J*= 13.9 Hz, $C\underline{H}_cH_d$), 2.65 (1H, dd, *J*= 14.4 Hz, *J*= 1.0 Hz, $C\underline{H}_eH_f$), 2.79 (1H, d, *J*= 11.2 Hz, $CH_a\underline{H}_b$), 2.87 (1H, d, *J*= 13.9 Hz, $CH_c\underline{H}_d$), 3.04 (1H, d, *J*= 14.4 Hz, $CH_e\underline{H}_f$), 4.94 (1H, br. s, $C{=}C\underline{H}_aH_b$), 5.00 (1H, br. s, $C{=}CH_a\underline{H}_b$), 5.19 (1H, d, *J*= 12.2 Hz, $C\underline{H}_aH_bPh$), 5.24 (1H, d, *J*= 12.2 Hz, $CH_a\underline{H}_bPh$), 7.35 (5H, br. s, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.78 (t-Bu), 27.89 (t-Bu), 37.48 (CH_2), 38.10 (CH_2), 41.10 (CH_2), 56.24 ($C_{quat.}$, C4), 64.71 ($C_{quat.}$, C2), 67.40 (CH_2Ph), 82.68 ($C_{quat.}$, t-Bu), 83.95 ($C_{quat.}$, t-Bu), 117.30 ($C{=}\underline{C}H_2$), 128.28 (CH), 128.50 (CH), 128.61 (CH), 135.00 ($C_{quat.}$, Ph), 138.36 ($\underline{C}{=}CH_2$), 148.80 (C=O, Boc), 167.54 (C=O), 169.86 (C=O), 170.10 (C=O), 177.59 (C=O). **IR (cm^{-1}) ν_{max} :** 1795, 1728. **MS: m/z (%):** (ES, Pos) no M^+, 316 (M^+-COOtBu, 100), 91 (15). **Chromatography**: 90/10 Hex/EtOAc R_f= 0.31.

6.2.2. Reduction to the pyrrolidine ring

1,4-Bis(t-butoxycarbonyl)-5-oxo-2-pyrrolidinecarboxylic acid 240

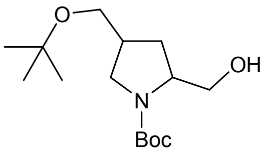
0.5 g of 2-benzyl 1,4-di-t-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (0.0012 mol) was dissolved in 5 ml of MeOH and 0.13 g (0.1 equiv.) of Pd-C was added and stirred overnight in a hydrogenation apparatus (5 bar H_2-gas). The reaction mixture was filtered over celite and washed with dichloromethane. The filtrate was evaporated under reduced pressure and 0.39 g of pure 1,4-bis(t-butoxycarbonyl)-5-oxo-2-pyrrolidinecarboxylic acid was obtained as a viscous oil (yield > 98 %; 58/42).



^{1}H-NMR (270 MHz, CDCl$_3$) δ: MAJOR: 1.49 (9H, s, t-Bu), 1.50 (9H, s, t-Bu), 2.31 (1H, ddd, *J*= 13.4 Hz, *J*= 9.1 Hz, *J*= 2.3 Hz, C<u>H</u>$_a$H$_b$ ring), 2.72 (1H, ddd, *J*= 13.4 Hz, *J*= 10.0 Hz, *J*= 9.9 Hz, CH$_a$<u>H</u>$_b$ ring), 3.60 (1H, dd, *J*= 10.2 Hz, *J*= 9.2 Hz, CH, C4), 4.69 (1H, dd, *J*= 9.6 Hz, *J*= 2.3 Hz, NCH, C2), 9.04 (1H, br. s, COO<u>H</u>); MINOR: 1.46 (9H, s, t-Bu), 1.49 (9H, s, t-Bu), 2.54-2.59 (2H, m, CH$_2$ ring), 3.46-3.51 (1H, m, CH, C4), 4.62 (1H, dd, *J*= 6.9 Hz, *J*= 6.9 Hz, NCH, C2), 9.04 (1H, br. s, COO<u>H</u>). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** MAJOR: 25.34 (CH$_2$ ring), 27.78 (2 x t-Bu), 49.43 (CH, C4), 57.16 (NCH, C2), 82.91 (C$_{quat.}$, t-Bu), 84.31 (C$_{quat.}$, t-Bu), 149.07 (C=O, Boc), 167.35 (C=O), 169.18 (C=O), 174.07 (C=O); MINOR: 24.69 (CH$_2$ ring), 27.89 (2 x t-Bu), 49.81 (CH, C4), 57.48 (NCH, C2), 83.11 (C$_{quat.}$, t-Bu), 84.31 (C$_{quat.}$, t-Bu), 149.07 (C=O, Boc), 166.50 (C=O), 169.04 (C=O), 174.44 (C=O). **IR (cm^{-1}) ν_{max} :** 3217 (br.), 1789, 1730. **MS: m/z (%):** (direct inlet) no M$^+$, 173 (8), 128 (52), 110 (22), 57 (55), 41 (100).

t-butyl 4-(t-butoxymethyl)-2-(hydroxymethyl)-1-pyrrolidinecarboxylate 247

0.4 g of 1,4-bis(t-butoxycarbonyl)-5-oxo-2-pyrrolidinecarboxylic acid was dissolved in 8 ml of dry THF and cooled to 0°C under a positive N_2-pressure. At this temperature 6.08 ml of BH_3-THF (1M in THF, 5 equiv.) was added and the reaction was stirred for 2 days while warming to room temperature. The reaction was quenched by the addition of MeOH until the bubbling stopped and an extra 5 ml of MeOH was added. The solvent was removed at the rotavapor and the residue was dissolved in 40 ml of MeOH and refluxed for 1 h. The solvent was removed once more and this procedure was repeated twice. The residue was dissolved in ether and washed with 0.5 N HCl solution (3 x 25 ml). The organic phase was dried with $MgSO_4$. After filtering off the drying agent and evaporating the solvent, 0.27 g of product was obtained. This was purified by column chromatography and 0.13 g of pure t-butyl 4-(t-butoxymethyl)-2-(hydroxymethyl)-1-pyrrolidinecarboxylate was obtained as an oil (yield = 37 %). Much of the compound was lost during column chromatography.

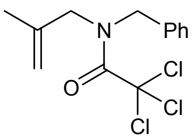


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.17 (9H, s, t-Bu), 1.47 (9H, s, t-Bu), 1.62-1.77 (1H, m, $C\underline{H}_aH_b$ ring), 1.80-1.91 (1H, m, $CH_a\underline{H}_b$ ring), 2.17-2.42 (1H, m, CH, C4), 3.20-3.29 (3H, m, $C\underline{H}_2$Ot-Bu, $C\underline{H}_aH_bN$ ring), 3.39-3.45 (1H, m, $NCH_a\underline{H}_b$ ring), 3.61-3.62 (2H, m, $C\underline{H}_2OH$), 4.02-4.03 (1H, m, NCH, C2), 4.64 (1H, br. s, O$\underline{H}$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.44 (t-Bu), 28.45 (t-Bu), 31.34 (CH_2 ring), 37.72 (CH, C4), 50.22 (CH_2N), 59.41 (NCH, C2), 63.20 ($\underline{C}H_2$Ot-Bu), 67.49 ($\underline{C}H_2OH$), 72.76 ($C_{quat.}$, $CH_2O\underline{C}(CH_3)_3$), 80.18 ($C_{quat.}$, $COO\underline{C}(CH_3)_3$), 157.09 (C=O, Boc); **^{13}C-NMR (68 MHz, C_6D_6) δ:** 27.46 (t-Bu), 28.48 (t-Bu), 31.21 (CH_2 ring), 37.93 (CH, C4), 50.49 (NCH_2), 60.00 (NCH, C2), 63.34 ($\underline{C}H_2OH$), 66.86 ($\underline{C}H_2$Ot-Bu), 72.34 ($C_{quat.}$, $CH_2O\underline{C}(CH_3)_3$), 79.66 ($C_{quat.}$, $COO\underline{C}(CH_3)_3$), 156.78 (C=O, Boc). **IR (cm^{-1}) ν_{max} :** 1694, 3429 (br. OH). **MS: m/z (%):** (ES, Pos) no M^+, 232 (20), 176 (100), 132 (55). **Chromatography**: Hex/EtOAc 50/50 R_f= 0.24.

6.3. Entry to 4-halomethyl pyrrolidine using the Kharasch reaction

N-Benzyl-2,2,2-trichloro-N-(2-methyl-2-propenyl)acetamide 275

1g of N-benzyl-2-methyl-2-propen-1-amine was dissolved in 10 ml of dry THF and 0.82 g (1.3 equiv.) triethyl amine was added. To this solution 1.51 g (1.3 equiv.) of trichloroacetyl chloride in 2 ml of THF was slowly added under a N_2-atmosphere. The reaction was heated under reflux overnight. After cooling, a saturated $NaHCO_3$ solution was added and the reaction mixture was extracted with diethyl ether. The combined organic phases were dried with $MgSO_4$ overnight. Filtering off the drying agent and evaporating the solvent gave 2.17 g of the crude product which was purified by column chromatography. 1.52 g of pure N-benzyl-2,2,2-trichloro-N-(2-methyl-2-propenyl)acetamide was obtained as a liquid (yield = 80 %; 57/43).

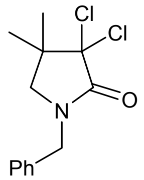


^{1}H-NMR (270 MHz, $CDCl_3$) δ: $\underline{\text{MAJOR}}$, *MINOR*, not assigned: *1.63* (3H, s, CH_3), $\underline{1.71}$ (3H, s, CH_3), $\underline{3.93}$ (2H, s, NCH_2), *4.19* (2H, s, NCH_2), *4.66* (2H, s, NCH_2Ph), $\underline{4.73}$ (1H, s, $C=C\underline{H}_aH_b$), *4.89* (1H, s, $C=C\underline{H}_aH_b$), $\underline{4.93}$ (1H, s, $C=CH_a\underline{H}_b$), $\underline{4.96}$ (2H, s, NCH_2Ph), *5.06* (1H, s, $C=CH_a\underline{H}_b$), 7.23-7.37 (5H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** $\underline{\text{MAJOR}}$, *MINOR*, not assigned: 19.93 (CH_3), *50.37* (NCH_2Ph), $\underline{51.90}$ (NCH_2Ph), $\underline{52.06}$ (NCH_2), *53.94* (NCH_2), 93.12 ($\underline{C}Cl_3$), $\underline{112.77}$ ($C=\underline{C}H_2$), *113.49* ($C=\underline{C}H_2$), 126.90 (CH), 127.72 (CH), 128.68 (CH), $\underline{135.09}$ ($C_{quat.}$, Ph), *135.79* ($C_{quat.}$, Ph), 138.67 ($\underline{C}=CH_2$), $\underline{160.63}$ (C=O), *160.97* (C=O). **IR (cm^{-1}) ν_{max} :** 1682, 1605, 1496. **MS: m/z (%):** (ES, Pos) 306/308/310/312 (100), 145 (42), 91 (25).

1-Benzyl-3,3-dichloro-4,4-dimethyl-2-pyrrolidinone 277

25 ml of xylene was flushed with N_2-gas during 1 h to remove the present O_2. 0.25 g of N-benzyl-2,2,2-trichloro-N-(2-methyl-2-propenyl)acetamide was dissolved in this solution and 0.1 g Cu(I)Cl (1.3 equiv.) was added. The mixture was heated under reflux for 1 day but analysing the

reaction on TLC showed no significant reaction. Another 0.1 g of Cu(I)Cl (1.3 equiv.) was added and the mixture was heated under reflux for two days. On TLC the starting product had disappeared, the suspension was filtered over celite and the solvent was removed under reduced pressure. The crude product was purified by column chromatography and 0.1 g of 1-benzyl-3,3-dichloro-4,4-dimethyl-2-pyrrolidinone was obtained as an oil (yield = 45 %).

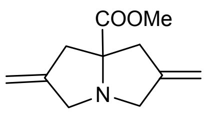


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.22 (6H, s, CH_3), 3.02 (2H, s, NCH_2), 4.51 (2H, s, CH_2Ph), 7.23-7.35 (5H, m, Ph), **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 22.62 (CH_3), 45.39 ($C_{quat.}$), 47.65 (NCH_2), 55.61 (CH_2Ph), 91.91 ($\underline{C}Cl_2CO$), 128.07 (CH), 128.28 (CH), 128.84 (CH), 134.89 ($C_{quat.}$, Ph), 166.66 (C=O). **IR (cm^{-1}) ν_{max} :** 1725 **MS: m/z (%):** (ES, Pos) 272/274/276 (100).

6.4. Entry to the pyrrolizine skeleton

Methyl 2,6-dimethylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate 300

1g of methyl [(phenylmethylidene)amino]acetate (5.7 mmol) was dissolved in 10 ml of dry THF and stirred under a nitrogen atmosphere. 0.71 g Of KOtBu (1.1 equiv.) was added and the reaction mixture was heated at 40°C after which 0.81 g (1.1 equiv.) 3-chloro-2-chloromethyl-1-propene was added. After 30 minutes of reaction, another amount of 0.71 g of KOtBu (1.1 equiv.) and 0.81 g of 3-chloro-2-chloromethyl-1-propene (1.1 equiv.) was added. After 45 minutes the reaction was quenched with 10 ml of water and the reaction mixture was extracted with diethyl ether (3 x 20 ml). The organic layers were combined and dried with $MgSO_4$. After filtering off the latter, the filtrate was evaporated under reduced pressure. The residue was dissolved in a mixture of 20 ml of diethyl ether and 20 ml of oxalic acid (sat.). The reaction mixture was stirred for 1 hour after which it was extracted with diethyl ether (2 x 20 ml). The water layer was basified using a saturated $NaHCO_3$ solution and stirred during 3 hours. The reaction mixture was subsequently extracted with EtOAc and the combined organic layers were dried with $MgSO_4$. After filtration the filtrate was evaporated under reduced pressure. The resulting oil was distilled using a Kögelruhr distillation (0.1 mbar, 90°C) and 0.44 g of methyl 2,6-dimethylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate was obtained as a clear oil (yield = 40 %).

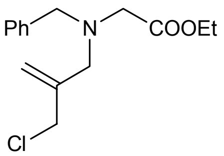


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 2.59 (2H, dd, J= 16.6 Hz, J= 1.2 Hz, 2 x $C\underline{H}_aH_b$), 2.99 (2H, dd, J= 16.6 Hz, J= 1.7 Hz, 2 x $CH_a\underline{H}_b$), 3.26 (2H, dd, J= 14.9 Hz, J= 1.8 Hz, 2 x $C\underline{H}_cH_d$), 3.74 (3H, s, $COOCH_3$), 3.82 (2H, br. d, J= 14.9 Hz, 2 x $CH_c\underline{H}_d$), 4.93-5.00 (4H, m, 2x C=CH_2). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 40.95 ($C_{quat.}\underline{C}H_2$), 52.52 ($COO\underline{C}H_3$), 59.44 ($NCH_2$), 76.44 ($C_{quat.}$), 106.88 (C=$\underline{C}H_2$), 147.11 ($\underline{C}$=$CH_2$), 175.18 (C=O). **IR (cm^{-1}) ν_{max} :** 1734. **MS: m/z (%):** (GC) 193 (M^+, 1), 134 (100), 132 (9), 94 (9), 53 (4), 44 (5), 40 (23).

6.5. Entry to 4-halomethyl pyrrolidine from ethyl glycinate

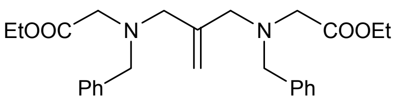
Ethyl {benzyl[2-(chloromethyl)-2-propenyl]amino}acetate 305

To a solution of 9.72 g $ClCH_2C{=}CH_2CH_2Cl$ (1.5 equiv.) in 100 ml of dry THF under nitrogen, a solution containing 10 g ethyl (benzylamino)acetate (0.0518 mol) and 5.24 g triethylamine (1 equiv.) was added dropwise at room temperature. After the addition was complete the reaction was heated under reflux for 2 days. A saturated $NaHCO_3$ solution was added (50 ml) and the mixture was extracted with diethyl ether (3x 100 ml). Drying the organic phase with $MgSO_4$ overnight and filtering off the latter, the organic phase was evaporated and 15.92 g of crude end product was obtained. This oil was purified by flash chromatography and 10 g of ethyl {benzyl[2-(chloromethyl)-2-propenyl]amino}acetate (yield 69 %) was obtained. A minor fraction of 1.58 g of diethyl 3,7-diaza-3,7-dibenzyl-5-methylene nona-1,9-dioate was also isolated as an oil (0.036 mol, yield 7%).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.25 (3H, *J*= 7.3 Hz, $COOCH_2CH_3$), 3.26 (2H, s, CH_2), 3.38 (2H, s, CH_2), 3.78 (2H, s, CH_2), 4.13 (2H, q, *J*= 7.3 Hz, $COOC\underline{H_2}CH_3$), 4.16 (2H, s, CH_2Cl), 5.21 (1H, s, $C{=}C\underline{H_a}H_b$), 5.28 (1H, s, $C{=}CH_a\underline{H_b}$), 7.23-7.34 (5H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.25 ($COOCH_2\underline{C}H_3$), 45.79 (CH_2), 53.39 (CH_2), 56.62 (CH_2), 57.72 (CH_2), 60.11 ($O\underline{C}H_2CH_3$), 117.30 ($C{=}\underline{C}H_2$), 127.17 (CH), 128.30 (CH), 128.80 (CH), 138.70 ($C_{quat.}$), 143.11 ($C_{quat.}$), 171.01 ($\underline{C}OOCH_2CH_3$). **IR (cm^{-1}) ν_{max} :** 1737, 1495, 1603, 1649. **MS: m/z (%):** (ES, Pos) 284/282 (M^++1, 100). **Chromatography**: Hex/EtOAc 90/10 R_f= 0.34.

Diethyl 3,7-diaza-3,7-dibenzyl-5-methylene nona-1,9-dioate 306

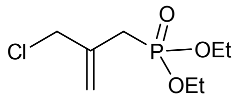


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.24 (6H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H_3}$), 3.24 (4H, s, NCH_2), 3.30 (4H, s, NCH_2), 3.75 (4H, NCH_2), 4.12 (4H, q, *J*= 7.1 Hz, $COOC\underline{H_2}CH_3$), 5.17 (2H, s, $C{=}C\underline{H_2}$), 7.22-7.30 (10H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.29 (CH_3), 53.55 (NCH_2), 57.16 (NCH_2), 57.61 (NCH_2), 59.96 ($O\underline{C}H_2CH_3$), 115.78 ($C{=}\underline{C}H_2$), 126.95 (CH), 128.17 (CH), 128.86 (CH), 139.19 ($C_{quat.}$), 144.63 ($\underline{C}{=}CH_2$), 171.39 (COOEt). **IR (cm^{-1}) ν_{max} :** 1739, 1453, 1495, 1603. **MS: m/z (%):** (ES, Pos) 439 (M^++H, 100). **Chromatography**: : Hex/EtOAc 90/10 R_f= 0.15.

6.5.1. Reactivity evaluation of 3-chloro-2-(chloromethyl)-1-propene

Diethyl 2-(chloromethyl)-2-propenylphosphonate 308a

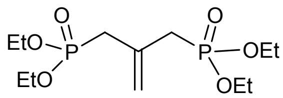
To 0.2 g 3-chloro-2-(chloromethyl)-1-propene, 0.29 g triethyl phosphite (1 equiv.) was added and the mixture was heated overnight at 90-100°C. Since the reaction was not completely selective the mixture was purified by distillation. 0.22 g of pure diethyl 2-(chloromethyl)-2-propenylphosphonate was obtained as an oil (yield = 59 %).



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.33 (6H, t, *J*= 7.1 Hz, OCH$_2$C$\underline{H}_3$), 2.76 (2H, dd, *J*= 21.9 Hz, *J*= 0.8 Hz, CH$_2$P), 4.06-4.17 (4H, m, OC$\underline{H}_2$CH$_3$), 4.21 (2H, dd, *J*= 2.1 Hz, *J*= 0.8 Hz, CH$_2$Cl), 5.19 (1H, dd, *J*= 5.6 Hz, *J*= 0.7 Hz, C=C$\underline{H}_a$H$_b$), 5.34-5.35 (1H, m, C=CH$_a\underline{H}_b$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 16.45 (d, *J*= 6.1 Hz, OCH$_2\underline{C}$H$_3$), 30.63 (d, *J*= 138 Hz, CH$_2$P), 48.16 (d, *J*= 2.4 Hz, CH$_2$Cl), 62.13 (d, *J*= 6.1 Hz, O$\underline{C}$H$_2$CH$_3$), 119.23 (d, *J*= 11 Hz, C=C$\underline{H}_2$), 136.41 (d, *J*= 11 Hz, $\underline{C}$=CH$_2$). **IR (cm^{-1}) ν_{max} :** 1249. **MS: m/z (%):** (ES, Pos) 229/227 (M$^+$+H, 100), 210/199 (40), 171/173 (30). **^{31}P-NMR (109 MHz, CDCl$_3$) δ:** 26.23 ppm. **bp. =** 78°C/0.01 mbar.

Diethyl 2-(diethylphosphonomethyl)-2-propenylphosphonate 309a

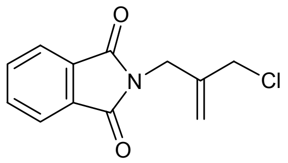
To 0.3 g of 3-iodo-2-(iodomethyl)-1-propene, 0.34 g of triethyl phosphite was added and heated at 90°C overnight. The reaction mixture was very clean and was only purified by column chromatography to remove the slight excess of triethyl phosphite. The product was isolated as an oil (yield = 93 %).



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.31 (6H, t, *J*= 7.1 Hz, OCH$_2$C$\underline{H}_3$), 1.32 (6H, t, *J*= 7.1 Hz, OCH$_2$C$\underline{H}_3$), 2.84 (4H, br. d, *J*= 23.4 Hz, CH$_2$P), 4.11 (8H, dq, *J*= 7.1 Hz, *J*= 7.0 Hz, COOC$\underline{H}_2$CH$_3$), 5.15 (2H, t, *J*= 5.5 Hz, C=C$\underline{H}_2$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 16.42 (COOCH$_2\underline{C}$H$_3$), 33.93 (d, *J*= 139.2 Hz, CH$_2$P), 62.05 (O$\underline{C}$H$_2$CH$_3$), 119.57 (t, *J*= 12.2 Hz, C=$\underline{C}$H$_2$), 131.05 (t, *J*= 11 Hz, $\underline{C}$=CH$_2$). **IR (cm^{-1}) ν_{max} :** 1243. **MS: m/z (%):** (ES, Pos) 329 (M$^+$+1, 100). **^{31}P-NMR (109 MHz, CDCl$_3$) δ:** 26.63 ppm. **Chromatography:** 100% EtOAc then 96/4 EtOAc/MeOH.

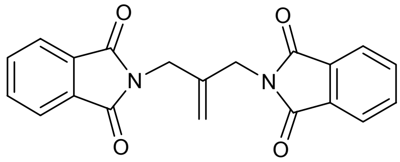
2-[2-(Chloromethyl)-2-propenyl]-1*H*-isoindole-1,2(2H)-dione 308b

2 g potassium phtalimide was dissolved in 40 ml of DMF, 2.02 g (1.5 equiv.) 3-chloro-2-(chloromethyl)-1-propene was added and the mixture was heated at 100°C overnight. The solvent was evaporated and 40 ml of dichloromethane was added. The organic layer was washed with 60 ml of brine and the water layer was extracted with dichloromethane (3 x 50 ml). The organic layers were combined and dried with $MgSO_4$. After filtration and evaporation of the solvent, the product starts to crystallise. Some diethyl ether was added and the product was filtered off. The crystals were washed with an extra amount of diethyl ether and the crude product was purified by column chromatography. The major fraction consists 0.6 g of 2-[2-(chloromethyl)-2-propenyl]-1H-isoindole-1,2(2H)-dione as a white powder (yield = 23%). The minor fraction was identified as 2-{2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-propenyl}-1H-isoindol-1,2(2H)-dione and 0.1 g isolated as a white powder (yield = 3 %). Although the R_f values were chosen very high, severe losses occurred when performing the column chromatography.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.12 (2H, s, CH_2), 4.41 (2H, s, CH_2), 5.18 (1H, s, $C{=}C\underline{H}_aH_b$), 5.33 (1H, s, $C{=}CH_a\underline{H}_b$), 7.27-7.77 (2H, m, CH, Ph), 7.85-7.89 (2H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 39.91 (NCH_2), 46.04 (CH_2Cl), 117.48 ($C{=}\underline{C}H_2$), 123.43 (CH), 131.95 ($C_{quat.}$), 134.18 (CH), 139.40 ($\underline{C}{=}CH_2$), 167.85 (C=O). **IR (cm^{-1}) ν_{max} :** (KBr) 1714. **MS: m/z (%):** (ES, Pos) 238/236 (M^++1, 100), 200 (73). **Chromatography:** 50/50 Hex/EtOAc R_f= 0.61. **Mp=** 88.8 °C.

2-{2-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-2-propenyl}-1*H*-isoindol-1,2(2H)-dione 309b

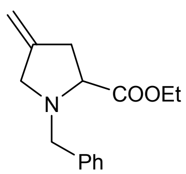


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.35 (4H, s, NCH_2), 5.12 (2H, s, $C{=}C\underline{H}_2$), 7.71-7.74 (4H, m, CH, Ph), 7.84-7.87 (4H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 40.56 (NCH_2), 115.04 ($C{=}\underline{C}H_2$), 123.41 (CH), 132.00 ($C_{quat.}$), 134.07 (CH, Ph), 138.00 ($\underline{C}{=}CH_2$), 167.90 (C=O). **IR (cm^{-1}) ν_{max} :** (KBr) 1714. **MS: m/z (%):** (ES, Pos) 347 (M^++1, 100). **Chromatography:** 50/50 Hex/EtOAc R_f= 0.39. **Mp=** 212.8 °C.

6.5.2. Synthesis of 4-methylene-2-pyrrolidinecarboxylate and its analogues

Ethyl 1-benzyl-4-methylene-2-pyrrolidinecarboxylate 311

3 g ethyl {benzyl[2-(chloromethyl)-2-propenyl]amino}acetate was dissolved in 45 ml of dry THF and cooled to -78°C. At this temperature and under a nitrogen atmosphere, 15.98 ml of LiHMDS solution (1.5 equiv.) was added. After the addition the reaction was allowed to warm to 0°C keeping the flask in the acetone bath. After 3 h the temperature reached 0°C and the reaction was quenched by adding 5 ml of a saturated NH_4Cl/NH_4OH. An extra 30 ml of water was added and the reaction was extracted with 3x 50 ml of diethyl ether. The organic phase was dried with $MgSO_4$ overnight. After filtration and evaporation of the solvent 2.45g of pure ethyl 1-benzyl-4-methylene-2-pyrrolidinecarboxylate was obtained as an oil (0.01 mol, yield 94%).

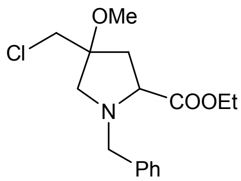


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.28 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.83 (1H, dd, *J*= 16.2 Hz, *J*= 7.6 Hz, $C\underline{H}_aH_b$), 2.66 (1H, dddd, *J*= 16.2 Hz, *J*= 7.4 Hz, *J*= 4.7 Hz, *J*= 2.6 Hz, $CH_a\underline{H}_b$), 3.09 (1H, ddd, *J*= 13.6 Hz, *J*= 2.3 Hz, *J*= 1Hz, $NC\underline{H}_aH_b$), 3.44 (1H, dd, *J*= 7.8 Hz, 7.5 Hz, NCH), 3.52 (1H, d, *J*= 12.9 Hz, $NC\underline{H}_aH_b$ Ph), 3.58 (1H, dd, *J*= 13.6 Hz, *J*= 1.4 Hz, $NCH_a\underline{H}_b$), 3.96 (1H, d, *J*= 12.9 Hz, $NCH_a\underline{H}_bPh$), 4.17 (2H, q, $COOC\underline{H}_2CH_3$), 4.86-4.89 (2H, m, $C{=}C\underline{H}_2$), 7.28-7.39 (5H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.25 ($COOCH_2\underline{C}H_3$), 36.42 (CH_2), 57.59 (NCH_2), 58.17 (NCH_2Ph), 60.54 ($COO\underline{C}H_2CH_3$), 65.43 (NCH), 105.78 ($C{=}\underline{C}H_2$), 127.17 (CH), 128.23 (CH), 129.02 (CH), 138.08 ($C_{quat.}$, Ph), 145.23 ($\underline{C}{=}CH_2$), 172.92

($\underline{C}OOCH_2CH_3$). **IR (cm^{-1}) ν_{max} :** 1731, 1454, 1495, 1604. **MS: m/z (%):** (GC) no M^+, 172 (M^+-COOEt, 100), 91 (84), 65 (7).

Ethyl 1-benzyl-4-(chloromethyl)-4-methoxy-2-pyrrolidinecarboxylate 320

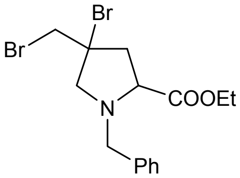
1.52 g ethyl 1-benzyl-4-methylene-2-pyrrolidinecarboxylate was dissolved in 30 ml of dry methanol and cooled to -10°C in an ice bath (after the addition of NaCl). 0.59 g of trichloroisocyanuric acid (0.4 equiv.) was added in one portion and stirring was continued for 30 min. The reaction was quenched with 5 ml of saturated Na_2SO_3 solution and after stirring for 2 min., the suspension was filtered over celite and washed with methanol. The filtrate was evaporated and dissolved in diethyl ether. The organic phase was extracted with 2x 30 ml of a 2N HCl solution. The water phase was subsequently basified with saturated $NaHCO_3$ and extracted with dichloromethane (3x 50 ml). The organic layer was dried using $MgSO_4$ overnight. Filtration and evaporation of the solvent gave 1.45 g of ethyl 1-benzyl-4-(chloromethyl)-4-methoxy-2-pyrrolidinecarboxylate as an oil (0.0046 mol, yield 75%; 78/22).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.26 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.03 (1H, dd, *J*= 13.7 Hz, *J*= 7.3 Hz, $C\underline{H}_aH_bCH$), 2.31 (1H, dd, *J*= 13.7 Hz, *J*= 8.4 Hz, $CH_a\underline{H}_bCH$), 2.59 (1H, d, *J*= 10.2 Hz, $C\underline{H}_aH_bN$), 3.09 (1H, d, *J*= 10.2 Hz, $CH_a\underline{H}_bN$), 3.24 (3H, s, OCH_3), 3.49-3.56 (1H, m, NC$\underline{H}$), 3.56 (1H, d, *J*= 13.3 Hz, $NC\underline{H}_aH_bPh$), 3.73 (1H, d, *J*= 12.0 Hz, $C\underline{H}_aH_bCl$), 3.80 (1H, d, *J*= 12.0 Hz, $CH_a\underline{H}_bCl$), 3.93 (1H, d, *J*= 13.3 Hz, $NCH_a\underline{H}_bPh$), 4.14 (2H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 7.25-7.32 (5H, m, CH, Ph); MINOR: 1.28 (3H, t, *J*= 7.0 Hz, $COOCH_2C\underline{H}_3$), 2.27-2.32 (2H, m, $C\underline{H}_2CH$ ring), 2.48 (1H, d, *J*= 10.8 Hz, $NC\underline{H}_aH_b$), 3.18 (1H, d, *J*= 10.8 Hz, $NCH_a\underline{H}_b$), 3.29 (3H, s, $OC\underline{H}_3$), 3.43 (1H, d, *J*= 13.3 Hz, $NC\underline{H}_aH_bPh$), 3.49-3.58 (3H, m, NCH + CH_2Cl), 4.02 (1H, d, *J*= 13.3 Hz, $NCH_a\underline{H}_bPh$), 4.12-4.21 (2H, m, $COOC\underline{H}_2CH_3$), 7.25-7.32 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 14.09 (CH_3), 37.94 (CH_2CH), 47.30 (CH_2), 50.71 (OCH_3), 57.85 (CH_2), 60.02 (CH_2), 60.67 (CH_2), 64.04 (NCH), 82.89 ($C_{quat.}$), 127.00 (CH), 128.16 (CH), 128.75 (CH), 137.65 ($C_{quat.}$, Ph), 172.76 (COOEt); MINOR: 13.96 (CH_3), 37.85 (CH_2), 48.30 (CH_2), 51.00 (CH_3), 57.47 (CH_2), 59.28 (CH_2), 60.61 (CH_2), 64.37 (NCH), 82.89 ($C_{quat.}$), 127.96 (CH), 128.30 (CH), 128.64 (CH), 137.84 ($C_{quat.}$), 172.42 (COOEt). **IR (cm^{-1}) ν_{max} :** 1742, 1454, 1495, 1604. **MS: m/z (%):** MAJOR: (GC) no M^+, 262 (M^+-Cl, 8), 241 (10), 240 (57), 239 (29), 238 (100), 206 (8), 192 (4), 92 (11), 91 (91), 65 (8); MINOR: (GC) no M^+, 262 (M^+-Cl, 6), 241 (9), 240 (58), 239 (28), 238 (100), 206 (8), 92 (11), 91 (91), 65 (8). **Chromatography:** EtOAc/Hex 70/30 R_f= 0.13.

Ethyl 1-benzyl-4-bromo-4-(bromomethyl)-2-pyrrolidinecarboxylate 316

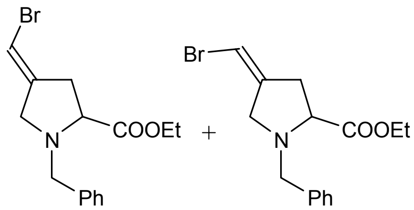
A solution of 0.41 g HBr (1.2 equiv., 48% in water) was added to 0.5 g ethyl 1-benzyl-4-methylene-2-pyrrolidinecarboxylate in 5 ml of dichloromethane. After stirring for 5 min. at 0°C, 0.34 g of bromine (1.05 equiv.) in 1 ml of dichloromethane was added. The reaction mixture was stirred for 4 h at room temperature. 2 ml of a saturated $NaHSO_3$ and 10 ml of saturated $NaHCO_3$ was added and the reaction was extracted using dichloromethane. After drying the organic phase and filtering off the $MgSO_4$ the filtrate was evaporated and 0.78 g of pure ethyl 1-benzyl-4-bromo-4-(bromomethyl)-2-pyrrolidinecarboxylate was obtained as a yellow clear oil (yield = 98%; 51/49).



^{1}H-NMR (270 MHz, CDCl$_3$) δ: MAJOR: 1.25 (3H, t, *J*= 7.3 Hz, $COOCH_2C\underline{H}_3$), 2.59 (1H, dd, *J*= 14.2 Hz, *J*= 8.3 Hz, $CHC\underline{H}_aH_b$), 2.69 (1H, dd, *J*= 14.2 Hz, *J*= 7.5 Hz, $CHCH_a\underline{H}_b$), 3.00 (1H, d, *J*= 11.2 Hz, $NC\underline{H}_aH_b$), 3.39 (1H, d, *J*= 11.2 Hz, $NCH_a\underline{H}_b$), 3.81-3.93 (3H, m, NCH, CH_2Br), 3.65 (1H, d, *J*= 13.5 Hz, $NC\underline{H}_aH_bPh$), 4.07 (1H, d, *J*= 13.5 Hz, $NCH_a\underline{H}_bPh$), 4.15 (2H, q, *J*= 7.3 Hz, $COOC\underline{H}_2CH_3$), 7.27-7.39 (5H, m, CH, Ph); MINOR: 1.29 (3H, t, *J*= 7.1 Hz, $COOCH_2\underline{C}H_3$), 2.76 (1H, dd, *J*= 15.0 Hz, *J*= 5.7 Hz, $NCHC\underline{H}_aH_b$), 2.85 (1H, dd, *J*= 15.0 Hz, *J*= 9.2 Hz, $NCHCH_a\underline{H}_b$), 3.17 (1H, d, *J*= 11.9 Hz, $NC\underline{H}_aH_b$), 3.53 (1H, dd, *J*= 9.2 Hz, *J*= 5.7 Hz, NCH), 3.58 (1H, d, *J*= 11.9 Hz, $NCH_a\underline{H}_b$), 3.81-3.93 (2H, m, CH_2Br), 3.76 (1H, d, *J*= 13.2 Hz, $NC\underline{H}_aH_bPh$), 4.15 (1H, d, *J*= 13.2 Hz, $NCH_a\underline{H}_bPh$), 4.21 (2H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 7.27-7.39 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** MAJOR: 14.21 (CH_3), 40.65 (CH_2Br), 44.89 ($NCH\underline{C}H_2$), 57.05 (NCH_2), 60.97 ($COO\underline{C}H_2CH_3$), 64.08 ($C_{quat.}$), 64.78 (NCH), 65.61 (NCH_2), 127.24 (CH), 128.28 (CH), 128.62 (CH), 138.09 ($C_{quat.}$), 172.14 ($\underline{C}OOCH_2CH_3$); MINOR: 14.18 (CH_3), 41.24 (CH_2Br), 44.33 ($NCH\underline{C}H_2$), 58.47 (NCH_2), 60.93 ($COO\underline{C}H_2CH_3$), 63.65 ($C_{quat.}$), 65.14 (NCH), 65.71 (NCH_2), 127.24 (CH), 128.28 (CH), 128.62 (CH), 137.75 ($C_{quat.}$), 172.52 ($\underline{C}OOEt$). **IR (cm^{-1}) ν_{max} :** 1736. **MS: m/z (%):** (direct inlet) 334/332/330 (M^+-COOEt, 100), 172 (6), 91 (54).

Ethyl (4 E/Z)-1-benzyl-4-(bromomethylene)-2-pyrrolidinecarboxylate 318a,b

Ethyl 1-benzyl-4-bromo-4-(bromomethyl)-2-pyrrolidinecarboxylate (0.25 g, 0.00062 mol) was dissolved in 5 ml of dry THF. The reaction was kept under a nitrogen atmosphere while adding 0.08 g of KOtBu (1.1 equiv.). The reaction was heated under reflux for 1 day after which 10 ml of $NaHCO_3$ solution was added and the reaction mixture was extracted with diethyl ether. After drying the organic phase and filtering off the $MgSO_4$, the solvent was removed under reduced pressure. The resulting oil was purified by means of flash chromatography and 0.1 g of ethyl (4 E/Z)-1-benzyl-4-(bromomethylene)-2-pyrrolidinecarboxylate was obtained as an oil (yield = 50%; 59/41).

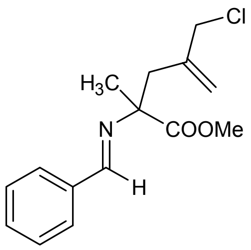


^{1}H-NMR (270 MHz, CDCl$_3$) δ: $\underline{\text{MAJOR}}$, *MINOR*: *$\underline{1.25\text{-}1.31}$* (3H, m, $COOCH_2C\underline{H}_3$), *$\underline{2.62\text{-}2.69}$* (1H, m, $C\underline{H}_aH_bCHN$), *$\underline{2.77\text{-}2.89}$* (1H, m, $CH_a\underline{H}_bCHN$), *3.06* (1H, br. d, *J*= 13.5 Hz, $NC\underline{H}_aH_b$ ring), $\underline{3.16}$ (1H, br. d, *J*= 15.2 Hz, $NC\underline{H}_aH_b$ ring), *$\underline{3.47\text{-}3.69}$* (3H, m, NCH, $CH_a\underline{H}_bCHN$, $C\underline{H}_aH_bPh$), *3.96* (1H, d, *J*= 12.9 Hz, $CH_a\underline{H}_bPh$), $\underline{3.97}$ (1H, d, *J*= 13.2 Hz, $CH_a\underline{H}_bPh$), *$\underline{4.13\text{-}4.23}$* (2H, m, $COOC\underline{H}_2CH_3$), $\underline{5.94}$ (1H, s, C=C$\underline{H}$Br), *5.97* (1H, s, C=C$\underline{H}$Br), *$\underline{7.26\text{-}7.35}$* (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** MAJOR: 14.37 (CH_3), 36.31 ($NCH\underline{C}H_2$), 57.66 (NCH_2), 57.96 (NCH_2), 60.88 ($O\underline{C}H_2CH_3$), 65.72 (NCH), 97.21 (C=$\underline{C}$HBr), 127.42 (CH), 128.46 (CH), 129.03 (CH), 137.86 ($C_{quat.}$), 142.98 ($\underline{C}$=CHBr), 172.54 ($\underline{C}OOEt$); MINOR: 14.37 (CH_3), 36.90 ($NCH\underline{C}H_2$), 57.39 (NCH_2), 58.08 (NCH_2), 60.88 ($O\underline{C}H_2CH_3$), 64.65 (NCH), 98.24 (C=$\underline{C}$HBr), 127.42 (CH), 128.46 (CH), 129.03 (CH), 137.74 ($C_{quat.}$), 142.83 ($\underline{C}$=CHBr), 172.54 ($\underline{C}$OOEt). **IR (cm^{-1}) ν_{max} :** 1729, 1742. **MS: m/z (%):** MAJOR: (GC) no M^+, 252/250 (M^+-COOEt, 100), 91 (64). MINOR: (GC) no M^+, 252/250 (M^+-COOEt, 100), 91 (62).

6.6. Entry to 4-halomethyl pyrrolidine form methyl 2-amino-propanoate

Methyl 4-(chloromethyl)-2-methyl-2-{[(E)-phenylmethylidene]amino}-4-pentenoate 329

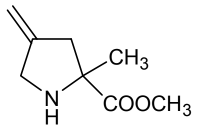
To a solution of 2.77 g methyl 2-{[(E)-phenylmethylidene]amino}propanoate in 30 ml of dry THF under a nitrogen atmosphere, 1.79 g of KOtBu (1.1 equiv.) was added and stirred at room temperature. After 20 min., 2.08 g $ClCH_2C{=}CH_2CH_2Cl$ (1.1 equiv.) was added and stirring was continued for 3 h. A $NaHCO_3$ solution was added (10 ml) and the reaction mixture was extracted with diethyl ether (3x 50 ml). Drying the organic phase ($MgSO_4$) overnight and filtering off the $MgSO_4$ led after evaporation of the solvent to 2.97 g methyl 4-(chloromethyl)-2-methyl-2-{[(E)-phenylmethylidene]amino}-4-pentenoate as an oil (0.0106 mol, yield 74%).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.53 (3H, s, CH_3), 2.74 (1H, d, *J*= 14.0 Hz, $C\underline{H}_aH_b$), 2.94 (1H, d, *J*= 14 Hz, $CH_a\underline{H}_b$), 3.73 (3H, s, $COOCH_3$), 4.17 (2H, s, CH_2Cl), 5.06 (1H, s, $C{=}C\underline{H}_aH_b$), 5.29 (1H, s, $C{=}CH_a\underline{H}_b$), 7.41-7.44 (3H, m, CH Ph), 7.74-7.77 (2H, m, CH Ph), 8.27 (1H, s, C$\underline{H}$=N). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 23.49 (CH_3), 43.41 ($\underline{C}H_2C{=}CH_2$), 49.15 (CH_2Cl), 52.06 ($COO\underline{C}H_3$), 68.57 ($C_{quat.}$), 118.99 ($C{=}\underline{C}H_2$), 128.28 (CH, Ph), 128.61 (CH, Ph), 130.99 (CH, Ph), 136.21 ($C_{quat.}$), 141.81 ($C_{quat.}$), 160.02 ($\underline{C}$=N), 173.85 ($\underline{C}$OOMe). **IR (cm^{-1}) ν_{max} :** 1729 (COOMe), 1643 (C=N). **MS: m/z (%):** (GC) no M^+, 244 (M^+-Cl, 100), 220 (22), 190 (41), 143 (29), 121 (33).

Methyl 2-methyl-4-methylene-2-pyrrolidinecarboxylate 322

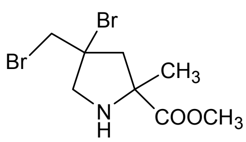
2.82 g methyl 4-(chloromethyl)-2-methyl-2-{[(E)-phenylmethylidene]amino}-4-pentenoate was dissolved in 30 ml of dichloromethane and 30 ml of saturated oxalic acid (in H_2O) was added and the solution stirred at room temperature for 1 h. The reaction mixture was extracted with 2 x 30 ml of dichloromethane. The organic phase contains benzaldehyde and is of no further use. The water phase was basified with a saturated K_2CO_3 solution and stirred at room temperature for 20 min. The water layer was extracted with 3 x 60 ml of dichloromethane and the organic phase was dried. Filtering off the $MgSO_4$ and evaporating the solvent gave 1.51 g of methyl 2-methyl-4-methylene-2-pyrrolidinecarboxylate as an oil which crystallises at -18°C but melts at room temperature (9.7 mmol, yield 96%).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.58 (3H, s, CH_3), 2.54 (1H, d, *J*= 16.2 Hz, $C\underline{H}_aH_b$), 2.91 (1H, d, *J*= 16.2 Hz, $CH_a\underline{H}_b$), 3.78 (5H, s, $COOC\underline{H}_3$, $NC\underline{H}_2$), 4.92 (1H, s, $C{=}C\underline{H}_aH_b$), 4.99 (1H, s, $C{=}CH_a\underline{H}_b$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 24.85 (CH_3), 43.40 (CH_2 ring), 50.64 (NCH_2), 52.42 ($COO\underline{Me}$), 66.13 ($C_{quat.}$, C2), 105.86 ($C{=}\underline{C}H_2$), 147.47 ($\underline{C}{=}CH_2$), 176.89 ($\underline{C}OOMe$). **IR (cm^{-1}) ν_{max} :** 1732. **MS: m/z (%):** (GC) 155 (M^+, 1), 140 (M^+-CH_3, 1), 108 (2), 97 (8), 96 (100), 94 (12), 81 (18), 80 (12).

Methyl 4-bromo-4-(bromomethyl)-2-methyl-2-pyrrolidinecarboxylate 323

0.2 g methyl 2-methyl-4-methylene-2-pyrrolidinecarboxylate was dissolved in 3 ml of dichloromethane cooled to 0°C, after which 0.24 g of a HBr solution (1.1 equiv., 48% HBr in H_2O) was added and the mixture was stirred for 10 min. 0.23 g of bromine (1.1 equiv.) in 1 ml of dichloromethane was added and the reaction mixture was allowed to warm to room temperature overnight. After the addition of 5 ml of saturated $NaHCO_3$ solution and some drops of a saturated $NaHSO_3$ solution, the reaction mixture was extracted with 3 x 10 ml of dichloromethane. After drying the organic phase with $MgSO_4$, filtration and evaporation of the organic solvent 0.33 g (1.05 mmol, yield 81%; 72/28) of methyl 4-bromo-4-(bromomethyl)-2-methyl-2-pyrrolidinecarboxylate was obtained as an oil.



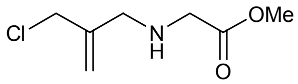
^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.43 (3H, s, CH_3), 2.35 (1H, d, *J*= 15.2 Hz, $C\underline{H}_aH_b$), 2.91 (1H, d, *J*= 15.2 Hz, $CH_a\underline{H}_b$), 3.10 (1H, br.s, NH), 3.34 (1H, d, *J*= 13.3 Hz, $NC\underline{H}_cH_d$), 3.41 (1H, d, *J*= 13.3 Hz, $NCH_c\underline{H}_d$), 3.79 (3H, s, $COOCH_3$), 3.92 (2H, s, CH_2Br); MINOR: 1.61 (3H, s, CH_3), 2.44 (1H, d, *J*= 15.5 Hz, $C\underline{H}_aH_b$), 2.95 (1H, d, *J*= 15.5 Hz, $CH_a\underline{H}_b$), 3.30 (1H, d, *J*= 12.2 Hz, $NC\underline{H}_cH_d$), 3.32 (1H, d, *J*= 12.2 Hz, $NCH_c\underline{H}_d$), 3.76 (3H, s, $COOCH_3$), 3.90 (2H, s, CH_2Br). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 27.17 (CH_3), 39.16 (CH_2Br), 51.93 (CH_2), 52.67 ($COO\underline{C}H_3$), 60.18 (NCH_2), 66.16 ($C_{quat.}$), 70.66 ($C_{quat.}$), 176.39 ($\underline{C}OOCH_3$); MINOR: 26.18 (CH_3), 39.48 (CH_2Br), 50.05 (CH_2), 52.67 ($COO\underline{C}H_3$), 61.19 (NCH_2), 66.56 ($C_{quat.}$), 70.66 ($C_{quat.}$), 176.19 ($\underline{C}OOCH_3$). **IR (cm^{-1}) ν_{max} :** 1734. **MS: m/z (%):** (GC) MAJOR: 258/256/254 (M^+-COOMe, 100), 176/174 (15), 96/94 (23); MINOR: 248/256/254 (M^+-COOMe, 100), 176/174 (16), 96/94 (25). **Bp.**= 105°C/0.5 mmHg.

6.7. Entry to the 3-methyleneazetidine

Methyl 3-aza-6-chloro-5-methylene hexanoate 334

Methyl glycine hydrochloride (1g, 0.0079 mol) was dissolved in 20 ml of dry THF using 1.61 g triethyl amine (2 equiv.). The formed triethyl amine hydrochloride crystallises in the reaction mixture as a white powder. 1.49 g $ClCH_2C{=}CH_2CH_2Cl$ dissolved in 2 ml of THF was added and the reaction mixture was heated under reflux overnight. The organic phase was washed with a saturated $NaHCO_3$ solution and dried with $MgSO_4$. After filtration and evaporation of the solvent

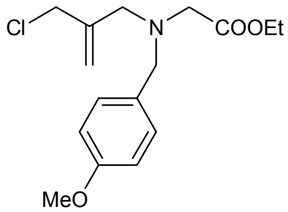
1.1 g of crude product was obtained. This amount was purified by flash chromatography and 0.6 g methyl 3-aza-6-chloro-5-methylene hexanoate was isolated as a viscous oil. It is important to mention the extreme lability of this compound and its easy polymerisation.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.66 (1H, br. s, NH), 3.39 (2H, s, CH_2), 3.41 (2H, s, CH_2), 3.74 (3H, s, $COOCH_3$), 4.14 (2H, s, CH_2), 5.19 (1H, s, C=C$\underline{H}_a$H$_b$), 5.27 (1H, s, C=CH$_a\underline{H}_b$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 46.34 (CH_2), 47.83 (CH_2), 49.63 (CH_2), 52.49 (CH_3), 120.68 (C=$\underline{C}H_2$), 139.21 ($\underline{C}$=CH_2), 169.49 ($\underline{C}OOCH_3$). **IR (cm^{-1}) ν_{max} :** 1750. **Chromatography:** EtOAc/Hex 70/30 R_f= 0.31.

Ethyl 3-aza-6-chloro-5-methylene-3-(4-methoxybenzyl)-hexanoate 341

To a flask containing 9.59 g $ClCH_2C{=}CH_2CH_2Cl$ in 50 ml of dry THF a solution of 11.4 g ethyl [(4-methoxybenzyl)amino]acetate (0.0511 mol) and 5.69 g triethyl amine (1.1 equiv.) in 70 ml of THF were slowly added. After adding of all the reagents, the reaction was refluxed for 2 days. The mixture is washed with $NaHCO_3$ and extracted with diethyl ether. After drying with $MgSO_4$ the solution was filtered and the filtrate evaporated. About 16 g of crude product was obtained which was purified by column chromatography in two portions. This led to 9.49 g of ethyl 3-aza-6-chloro-5-methylene-3-(4-methoxybenzyl)-hexanoate as an oil (yield 59 %).



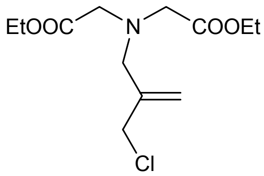
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.26 (3H, t, *J*= 7.1 Hz, COOCH$_2$C$\underline{H}_3$), 3.24 (2H, s, CH_2), 3.36 (2H, s, CH_2), 3.71 (2H, s, CH_2), 3.79 (3H, s, OCH_3), 4.14 (2H, q, *J*= 7.1 Hz, COOC$\underline{H}_2$CH$_3$), 4.15 (2H, s, CH_2), 5.21 (1H, s, C=C$\underline{H}_a$H$_b$), 5.28 (1H, s, C=CH$_a\underline{H}_b$), 6.86 (2H, d, *J*= 8.5 Hz, CH, Ph), 7.23 (2H, d, *J*= 8.5 Hz, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.29 (CH_3), 45.82 (CH_2), 53.30 (CH_2), 55.06 (OCH_3), 56.57 (CH_2), 57.21 (CH_2), 60.09 (O$\underline{C}$H$_2$CH$_3$), 113.73 (CH, Ph), 117.14 (C=CH_2), 130.03 (CH), 130.67 ($C_{quat.}$), 143.30 ($C_{quat.}$), 158.92 ($C_{quat.}$), 171.08 (COOEt). **IR (cm^{-1}) ν_{max} :** 1736, 1512, 1585, 1612. **MS: m/z (%):** (GC) 313/311 (M^+, 2), 276 (5), 240 (22), 238 (56), 222 (30), 190 (13), 122 (28), 121 (100), 91 (10), 78 (12), 77 (11). **Chromatography:** Hex/EtOAc 90/10 R_f= 0.29.

6.8. Entry to the 1-azabicyclo[2.2.1]heptane skeleton

Ethyl 3-aza-6-chloro-5-methylene-3-(ethylcarboxymethyl)hexanoate 345

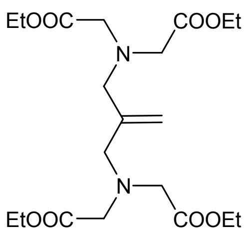
Ethyl 3-aza-6-chloro-5-methylene-3-(ethylcarboxymethyl)hexanoate can be prepared on a multi-gram scale. In an oven dried flask, a solution of 10 g (53.8 mmol) and 9.91 g $ClCH_2C{=}CH_2CH_2Cl$ (1.5 equiv.) in 110 ml of dry THF was stirred under a N_2-atmosphere after which 5.88 g triethylamine in 10 ml of THF is added dropwise. After all the triethyl amine is added, the solution is refluxed overnight. 70 ml of a 2N HCl solution was added and the reaction mixture was extracted twice with 100 ml of diethyl ether. The organic layer was dried overnight with

$MgSO_4$. After filtration and evaporation of the solvent, an oil was obtained which contained the pure ethyl 3-aza-6-chloro-5-methylene-3-(ethylcarboxymethyl)hexanoate and an excess of $ClCH_2C{=}CH_2CH_2Cl$ that could be removed under high vacuum. In total 11 g of ethyl 3-aza-6-chloro-5-methylene-3-(ethylcarboxymethyl)hexanoate (0.04 mol, yield 75%) was obtained as an oil. The remaining acidic water layer was basified with a 2N NaOH solution and extracted with 100 ml of dichloromethane. After drying the organic layer with $MgSO_4$, evaporation of the solvent gave 2.3 g of mainly dimer and some traces of ethyl 3-aza-6-chloro-5-methylene-3-(ethylcarboxymethyl)hexanoate. The latter was removed by means of flash chromatography and yielded diethyl 3,7-bis(ethylcarboxymethyl)-3,7-diaza-5-methylene nona-1,9-dioate as an oil (0.0047 mol, yield 9%).



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.27 (6H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 3.47 (2H, s, $NC\underline{H}_2C{=}CH_2$), 3.53 (4H, s, $NC\underline{H}_2COOEt$), 4.16 (4H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 4.19 (2H, s, CH_2Cl), 5.18 (1H, d, 1.3 Hz, $C{=}C\underline{H}_aH_b$), 5.28 (1H, br. s, $C{=}CH_a\underline{H}_b$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 14.27 ($COOCH_2\underline{C}H_3$), 45.73 ($N\underline{C}H_2C{=}CH_2$), 54.41 ($N\underline{C}H_2COOEt$), 56.94 ($\underline{C}H_2Cl$), 60.39 ($COO\underline{C}H_2CH_3$), 117.57 ($C{=}\underline{C}H_2$), 143.07 ($\underline{C}{=}CH_2$), 171.03 ($\underline{C}OOEt$). **IR (cm^{-1}) ν_{max} :** 1744. **MS: m/z (%):** (GC) 279/277 (M^+, 4), 242 (M^+-Cl, 30), 206 (58), 205 (20), 204 (100), 176 (10), 132 (23), 96 (18). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.43.

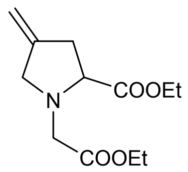
Diethyl 3,7-bis(ethylcarboxymethyl)-3,7-diaza-5-methylene nona-1,9-dioate 344



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.26 (12H, t, *J*= 7.3 Hz, $COOCH_2C\underline{H}_3$), 3.39 (4H, s, $NC\underline{H}_2C{=}CH_2$), 3.54 (8H, s, $NC\underline{H}_2COOEt$), 4.14 (8H, q, *J*= 7.3 Hz, $COOC\underline{H}_2CH_3$), 5.09 (2H, s, $C{=}C\underline{H}_2$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 14.29 ($COOCH_2\underline{C}H_3$), 54.32 ($N\underline{C}H_2COOEt$), 57.61 ($N\underline{C}H_2C{=}CH_2$), 60.20 ($COO\underline{C}H_2CH_3$), 115.78 ($C{=}\underline{C}H_2$), 144.69 ($\underline{C}{=}CH_2$), 171.34 ($\underline{C}OOEt$). **IR (cm^{-1}) ν_{max} :** 1744. **MS: m/z (%):** (ES, Pos) 431 (M^++H, 100), 343 (45), 190 (15). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.24.

Ethyl 1-(ethylcarboxymethyl)-4-methylene-2-pyrrolidinecarboxylate 346

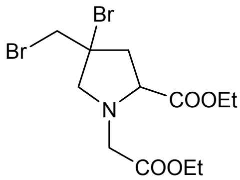
A solution of 5 g (0.018 mol) of ethyl 3-aza-6-chloro-5-methylene-3-(ethylcarboxymethyl)hexanoate was stirred in 70 ml of dry THF under nitrogen and at -78°C. At this temperature 27 ml (1.5 equiv.) of a 1N solution of LiHMDS was added and the solution was allowed to warm to 0°C in the acetone bath for 3h. The warming period of 3h is very important to obtain a pure end product. When the solution was allowed to warm to room temperature overnight, some side products were formed and it was necessary to purify the reaction mixture by means of flash chromatography. After the 3h warming period the reaction was quenched with a saturated solution of NH_4Cl/NH_4OH. After extraction with 3x 50 ml of diethyl ether the organic layer was dried with $MgSO_4$. Filtration and evaporation of the solvent gave 4 g (16.6 mmol, yield 92%) of pure ethyl 1-(ethylcarboxymethyl)-4-methylene-2-pyrrolidine-carboxylate as an oil.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.22 (6H, t, *J*= 6,7 Hz, $COOCH_2C\underline{H}_3$ x 2), 2.56-2.64 (1H, m, $C\underline{H}_aH_bCH$), 2.84 (1H, dd, *J*= 16.2 Hz, *J*= 7.7 Hz $CH_a\underline{H}_bCH$), 3.41 (1H, d, *J*= 17.2 Hz, $NC\underline{H}_aH_bCOOEt$), 3.42 (1H, d, *J*= 14.5 Hz, $C\underline{H}_aH_bC{=}CH_2$), 3.59 (1H, d, *J*= 17.2 Hz, $NCH_a\underline{H}_bCOOEt$), 3.70 (1H, dd, *J*= 7.6 Hz, *J*= 7.6 Hz, CH), 3.72 (1H, d, *J*= 14.5 Hz, $CH_a\underline{H}_bC{=}CH_2$), 4.09-4.17 (4H, m, 2 x $COOC\underline{H}_2CH_3$), 4.88 (2H, d, *J*= 1.7 Hz, $C{=}C\underline{H}_2$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.25 (2 x CH_3), 36.48 ($\underline{C}H_2CH$), 53.39 ($N\underline{C}H_2COOEt$), 57.29 ($\underline{C}H_2C{=}CH_2$), 60.57 ($COO\underline{C}H_2CH_3$), 60.72 ($COO\underline{C}H_2CH_3$), 63.99 (CH), 105.98 ($C{=}\underline{C}H_2$), 144.99 ($\underline{C}{=}CH_2$), 170.46 (C=O), 172.67 (C=O). **IR (cm^{-1}) ν_{max} :** 1736 (br.), **MS: m/z (%):** 241 (M^+, 4), 168 (M^+-COOEt, 100), 140 (12), 94 (16). **Chromatography**: 70/30 Hex/EtOAc R_f= 0.33.

Ethyl 4-bromo-4-(bromomethyl)-1-(ethylcarboxymethyl)-2-pyrrolidinecarboxylate 347

A solution of 0.26 g ethyl 1-(ethylcarboxymethyl)-4-methylene-2-pyrrolidinecrboxylate in 3 ml of dichloromethane was cooled to 0°C in an ice bath, then 0.2 g HBr solution (1.1 equiv., 48% HBr in H_2O) was added and the mixture was stirred for 15 min. 0.18 g of bromine (1.05 equiv.) in 1 ml of dichloromethane was added and the reaction mixture was allowed to warm to room temperature overnight. After the addition of 5 ml of saturated $NaHCO_3$ solution and some drops of a saturated $NaHSO_3$ solution, the reaction mixture was extracted with 3x 10 ml of dichloromethane. After drying the organic phase with $MgSO_4$ and evaporation of the organic solvent after filtration of the $MgSO_4$ gave 0.38g (0.00095 mol, yield 88%; 61/39) of ethyl 4-bromo-4-(bromomethyl)-1-(ethylcarboxymethyl)-2-pyrrolidinecarboxylate as an oil.

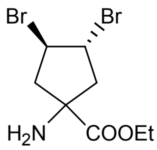


^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.28 (6H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.77 (1H, dd, *J*= 14.6 Hz, *J*= 3.1 Hz, $C\underline{H}_aH_bCH$), 2.95 (1H, dd, *J*= 14.6 Hz, *J*= 9.9 Hz, $CH_a\underline{H}_bCH$), 3.48 (1H, d, *J*= 10.8 Hz, $NC\underline{H}_aH_b$), 3.59 (1H, d, *J*= 10.8 Hz, $NCH_a\underline{H}_b$), 3.64-3.79 (2H, m, $NC\underline{H}_2COOEt$), 3.90-3.98 (3H, m, $C\underline{H}_2Br$, $NC\underline{H}$), 4.15-4.28 (4H, m, $COOC\underline{H}_2CH_3$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.23 ($COOCH_2\underline{C}H_3$), 39.60 (CH_2Br), 44.17 ($\underline{C}H_2CH$), 51.54 ($N\underline{C}H_2COOEt$), 60.59 ($COO\underline{C}H_2CH_3$), 61.08 ($COO\underline{C}H_2CH_3$), 62.18 (CH), 64.67 (NCH_2), 65.61 (C_{quat}), 170.71 (C=O), 172.61 (C=O). MINOR: 1.30 (6H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.61 (1H, dd, *J*= 14.1 Hz, *J*= 7.3 Hz, $C\underline{H}_aH_bCH$), 2.71 (1H, dd, *J*= 14.1 Hz, *J*= 7.3 Hz, $CH_a\underline{H}_bCH$), 3.54 (1H, d, *J*= 11.8 Hz, $NC\underline{H}_aH_b$), 3.69-3.72 (2H, m, $NC\underline{H}_2COOEt$), 3.87 (1H, d, *J*= 11.8 Hz, $NCH_a\underline{H}_b$), 3.90-3.98 (3H, m, $C\underline{H}_2Br$, $NC\underline{H}$), 4.15-4.28 (4H, m, $COOC\underline{H}_2CH_3$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.18 ($COOCH_2C\underline{H}_3$), 40.95 (CH_2Br), 44.69 ($\underline{C}H_2CH$), 57.07 ($N\underline{C}H_2COOEt$), 60.66 ($COO\underline{C}H_2CH_3$), 61.13 ($COO\underline{C}H_2CH_3$), 63.65 (CH), 65.95 (NCH_2), 65.53 ($C_{quat.}$), 170.31 (C=O), 172.05 (C=O). **IR (cm^{-1}) ν_{max} :** 1738. **MS: m/z (%):** (ES, Pos) 404/402/400 (M^++1, 100).

6.9. Entry to the 5-azabicyclo[2.1.1]hexane-1-carboxylate skeleton

Ethyl 1-amino-3,4-dibromocyclopentane carboxylate 357

The general procedure for the bromination of N-alkylbicyclo[3.2.0]hept-2-en-6-amines was used here. The hydrobromic salt could not be isolated and the reaction was worked up by performing an extraction with dichloromethane and $NaHCO_3$. Isolated yield = 86% (oil).

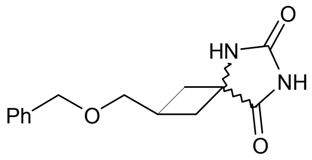


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.31 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 1.87 (2H, br. s, NH_2), 2.11 (1H, dd, *J*= 14.6 Hz, *J*= 6.5 Hz, $C\underline{H}_aH_b$), 2.46 (1H, dd, *J*= 14.2 Hz, *J*= 6.9 Hz, $C\underline{H}_cH_d$), 2.63 (1H, dd, *J*= 14.2 Hz, *J*= 7.9 Hz, $CH_c\underline{H}_d$), 3.12 (1H, dd, *J*= 14.6 Hz, *J*= 7.9 Hz, $CH_a\underline{H}_b$), 4.22 (2H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 4.41 (1H, br. q, *J*= 7.1 Hz, CHBr), 4.58 (1H, br. q, *J*= 7.3 Hz, CHBr). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.12 ($OCH_2C\underline{H}_3$), 47.56 (CH_2), 48.45 (CH_2), 53.58 (CHBr), 61.83 ($O\underline{C}H_2CH_3$), 63.36 ($C_{quat.}$ ring), 175.27 ($\underline{C}OOEt$). **IR (cm^{-1}) ν_{max} :** 1728. **MS: m/z (%):** (GC) no M^+, 244/242/240 (M^+-COOEt, 100), 236/238 (M^+-Br, 14), 162/160 (15), 82 (14), 81 (16), 80 (11).

6.10. Entry to 2,4-methanoproline using the Bucherer-Bergs synthesis

2-[(Benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione 360,361

5 g of 3-(benzyloxymethyl)cyclobutanone was dissolved in 75 ml of MeOH. A mixture of 1.86 g potassium cyanide (1.1 equiv.), 1.41 g ammonium chloride (1 equiv.) and 5.06 g ammonium carbonate (2 equiv.) was dissolved in 75 ml of distilled water. The two mixtures were added together and stirred for 2 days at room temperature. The solvent was reduced by evaporating to 60 % of its original volume. The remaining suspension (white powder) was extracted with dichloromethane and washed with 20 ml of water. The organic phases were dried with $MgSO_4$ overnight. After filtering off the drying agent and evaporation of the remaining solution, 6.42 g of crude product was obtained (a white powder that contained a small amount of starting material). The powder was filtered and washed thoroughly with hexane. The remaining starting material dissolved very well in this solvent whereas the end product did not. The white powder was dried under high vacuum and 5.82 g 2-[(benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione was obtained as a mixture of two isomers (3/1; white powder).

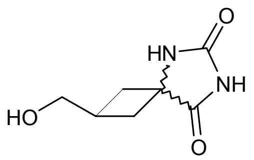


MAJOR (*cis*-isomer): **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 2.19-2.25 (2H, m, CH_2 ring), 2.59-2.75 (3H, m, CH_2 ring + CH ring), 3.46 (2H, d, *J*= 4.0 Hz, OC$\underline{H}_2$CH), 4.56 (2H, s, OCH_2Ph), 6.61 (1H, br. s, NH), 7.28-7.40 (5H, m, CH, Ph), 8.92 (1H, br. s, NH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.15 (CH ring), 34.86 (CH_2 ring), 59.41 ($C_{quat.}$), 72.06 (CH_2O), 73.13 (CH_2O), 127.74 (CH), 127.85 (CH), 128.52 (CH), 137.99 ($C_{quat.}$), 156.48 (C=O), 177.95 (C=O). **IR (cm^{-1}) ν_{max} :** 1773, 1726. **MS: m/z (%):** (direct inlet) 260 (M^+, 4), 222 (73), 156 (18), 99 (100), 84 (35). Crystallise MeOH/PET. **Mp.**= 158.1-158.7°C.

MINOR (*trans* isomer): **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 2.31-2.50 (4H, m, 2 x CH_2 ring), 2.60-2.74 (1H, m, CH ring), 3.64 (2H, d, *J*= 7.3 Hz, OCH_2), 4.52 (2H, s, OCH_2Ph), 6.76 (1H, br. s, NH), 7.25-7.46 (5H, m, CH, Ph), 9.19 (1H, br. s, NH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 26.86 (CH ring), 34.89 (CH_2 ring), 60.48 ($C_{quat.}$), 73.01 (O$\underline{C}$H$_2$CH), 73.15 (OCH_2Ph), 127.65 (CH), 127.74 (CH), 128.39 (CH), 138.20 ($C_{quat.}$, Ph), 157.27 (C=O), 177.12 (C=O). **IR (cm^{-1}) ν_{max} :** 1773, 1726. **MS: m/z (%):** 260 (M^+, 1), 204 (3), 91 (7), 86 (36), 84 (71), 51 (31), 49 (100).

2-(Hydroxymethyl)-5,7-diazaspiro[3.4]octane-6,8-dione 362

1g of 2-[(benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione was dissolved in 15 ml of ethanol and 1 ml of hydrochloric acid (1M solution) was added. After the addition of 0.41 g of Pd-C (0.1 equiv.) the suspension was put under a H_2-atmosphere (5 bar of H_2 pressure). The mixture was stirred vigorously overnight. After filtering the mixture over celite and washing it with ethanol, the solvent was removed by rotary evaporation and the white product was dried under high vacuum, 0.67 g 2-(hydroxymethyl)-5,7-diazaspiro[3.4]octane-6,8-dione was obtained as a white powder (yield > 98 %; 67/33). Remark: under neutral conditions no deprotection of the ether moiety was observed.



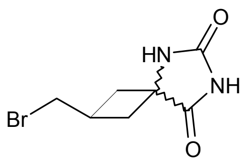
MAJOR: **^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ:** 2.07-2.14 (2H, m, CH_2 ring), 2.39-2.55 (1H, m, CH ring), 2.50-2.58 (2H, m, CH_2 ring), 3.52 (2H, d, *J*= 5.9 Hz, OCH_2). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 28.89 (CH ring), 35.38 (CH_2 ring), 59.91 ($C_{quat.}$, ring), 66.30 (CH_2OH), 158.86 (C=O), 182.31 (C=O).

MINOR: **^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ:** 2.31-2.39 (2H, m, CH_2 ring), 2.50-2.59 (3H, m, CH_2 ring + CH ring), 3.63 (2H, d, *J*= 7.3 Hz, OCH_2). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 29.25 (CH ring), 34.75 (CH_2 ring), 61.40 ($C_{quat.}$ ring), 65.71 (CH_2OH), 159.13 (C=O), 180.84 (C=O). **IR (cm^{-1}) ν_{max} :** 1731 (br. C=O), 3269 (br. OH). **MS: m/z (%):** (direct inlet) 171 (M^++1, 30), 102 (100). **Mp.**= 199.8-200.8°C.

There are two possible pathways to synthesise 1-amino-3-(bromomethyl)-cyclobutanecarboxylic acid hydrobromide

In the first and shortest way, 2-[(benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione was refluxed in a concentrated solution of hydrobromic acid for 7 h. By crystallization in water/MeOH the pure 1-amino-3-(bromomethyl)cyclobutanecarboxylic acid hydrobromide could be isolated with a yield of 55 %. If the reaction is stopped after 1.5 hours of reflux an interesting intermediate could be isolated. After this period an extraction was performed with diethyl ether. After shaking the two layers vigorously, many white crystals appeared between the organic and the water layer. These crystals dissolve better in the water phase than in the organic phase so an extra amount of water was added until all the crystals dissolved. The water layer was evaporated and 0.34 g of 2-(bromomethyl)-5,7-diazaspiro[3.4]octane-6,8-dione was found. Evaporation of the ether layer gave also a white crystal (after washing with ether, to remove benzyl bromide) leading to 0.07 g of 2-(bromomethyl)-5,7-diazaspiro[3.4]octane-6,8-dione. Total amount = 0.43 g (yield = 48 %; 75/25).

2-(Bromomethyl)-5,7-diazaspiro[3.4]octane-6,8-dione 366



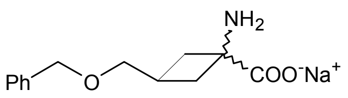
MAJOR: **^{1}H-NMR (270 MHz, DMSO-d_6) δ:** 1.94-2.02 (2H, m, CH_2 ring), 2.44-2.67 (3H, m, CH_2 ring + CH ring), 3.55 (2H, d, *J*= 7.3 Hz, CH_2Br), 8.22 (1H, br. s, NH), 10.63 (1H, br. s, NH). **^{13}C-NMR (68 MHz, DMSO-d_6) δ:** 28.54 (CH ring), 37.18 (CH_2 ring), 39.14 (CH_2Br), 56.33 ($C_{quat.}$), 155.88 (C=O), 178.34 (C=O).

MINOR: **^{1}H-NMR (270 MHz, DMSO-d_6) δ:** 2.17-2.41 (4H, m, 2 x CH_2 ring), 2.44-2.67 (1H, m, CH ring), 3.74 (2H, d, *J*= 8.3 Hz, CH_2Br), 8.43 (1H, br. s, NH), 10.63 (1H, br. s, NH). **^{13}C-NMR (68 MHz, DMSO-d_6) δ:** 29.00 (CH ring), 36.03 (CH_2 ring), 38.02 (CH_2Br), 58.00 ($C_{quat.}$), 156.00 (C=O), 177.59 (C=O). **IR (cm^{-1}) ν_{max} :** 1777 (C=O), 1730 (C=O). **MS: m/z (%):** (direct inlet) 234/232 (M^+, 34), 153 (100), 112 (74). **Mp.**: 229.5-230.4°C.

In the second procedure the purification of the end product was more convenient. In this case the hydantoin was first hydrolysed to the corresponding amino acid by refluxing 2-[(benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione in a 0.5N NaOH solution overnight. The white powder was dissolved in a concentrated hydrobromic acid solution and refluxed for 7 hours. The solvent was removed by evaporation and the product crystallised (white powder) and gave the 1-amino-3-(bromomethyl)cyclobutanecarboxylic acid hydrobromide (yield = 73 %).

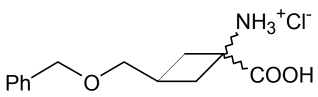
Sodium 1-amino-3-[(benzyloxy)methyl]cyclobutanecarboxylate 364

In a classical experiment, 5.81 g of 2-[(benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione was dissolved in 300 ml of 0.5 N NaOH solution and was refluxed overnight. The solvent (water) was evaporated and the pure sodium 1-amino-3-[(benzyloxy)methyl]cyclobutanecarboxylate was obtained (yield >98 %). In the ^{13}C spectrum the presence of sodium carbonate could be detected. This could easily be removed by adding hydrochloric acid (2N solution) and evaporating all the solvent. Then the pure 1-amino-3-[(benzyloxy)methyl]cyclobutanecarboxylic acid hydrochloride could be obtained (NaCl was still present).



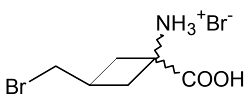
^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.55-1.62 (2H, m, CH_2 ring), 2.31-2.48 (3H, m, CH_2 ring + CH ring), 3.43 (2H, d, *J*= 6.4 Hz, $OC\underline{H}_2CH$), 4.42 (2H, s, $OC\underline{H}_2Ph$), 7.28-7.38 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** MAJOR: 27.11 (CH ring), 39.22 (CH_2 ring), 57.01 ($C_{quat.}$ ring), 73.80 (OCH_2Ph), 76.53 ($O\underline{C}H_2CH$), 129.46 (CH), 129.70 (CH), 129.91 (CH), 138.54 ($C_{quat.}$, Ph), 185.02 (COO^-Na^+); MINOR: 27.67 (CH ring), 36.83 (CH_2 ring), 57.66 ($C_{quat.}$), 73.80 (OCH_2Ph), 76.11 ($O\underline{C}H_2CH$), 129.46 (CH), 129.70 (CH), 129.91 (CH), 138.54 ($C_{quat.}$, Ph), 185.40 (COO^-Na^+). **MS: m/z (%):**(methyl ester, from reaction with diazomethane) (GC) 249 (M^+, 3), 234 (3), 190 (2), 147 (15), 101 (100), 91 (40).

1-Amino-3-[(benzyloxy)methyl]cyclobutanecarboxylic acid hydrochloride 370



(85/15) MAJOR: **^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ:** 2.14-2.21 (2H, m, CH_2 ring), 2.63-2.80 (3H, m, CH_2 ring + CH ring), 3.53 (2H, d, *J*= 5.0 Hz, $OC\underline{H}_2CH$), 4.49 (2H, s, OCH_2Ph), 7.36 (5H, s, CH, Ph). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 28.32 (CH ring), 33.80 (CH_2 ring), 54.91 ($C_{quat.}$), 73.83 (CH_2O), 74.19 (CH_2O), 129.37 (CH), 129.59 (CH), 129.75 (CH), 138.18 ($C_{quat.}$, Ph), 174.84 (COOH);
MINOR: **^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ:** 2.42-2.48 (2H, m, CH_2 ring), 2.63-2.80 (3H, m, CH_2 ring + CH ring), 3.59-3.60 (2H, m, $OC\underline{H}_2CH$), 4.78 (2H, s, OCH_2Ph), 7.36 (5H, s, CH, Ph). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 27.47 (CH ring), 32.75 (CH_2 ring), 56.26 ($C_{quat.}$ ring), 73.83 (CH_2O), 74.19 (CH_2O), 129.48 (CH), 129.59 (CH), 129.75 (CH), 138.18 ($C_{quat.}$, Ph), 174.84 (COOH). **IR (cm^{-1}) ν_{max} :** (KBr) 1732. **MS: m/z (%):(%):**(methyl ester, from reaction with diazomethane) (GC) 249 (M^+, 3), 234 (3), 190 (2), 147 (15), 101 (100), 91 (40).

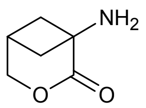
1-Amino-3-(bromomethyl)cyclobutanecarboxylic acid hydrobromide 365a



(67/33) MAJOR (*cis*-isomer): **^{1}H-NMR (270 MHz, D_2O) δ:** 2.18-2.27 (2H, m, CH_2 ring), 2.67-2.76 (2H, m, CH_2 ring), 2.92-2.95 (1H, m, CH ring), 3.53 (2H, d, *J*= 10.3 Hz, CH_2Br). **^{13}C-NMR (68 MHz, D_2O) δ:** 29.94 (CH ring), 35.26 (CH_2 ring), 38.46 (CH_2Br), 52.60 ($C_{quat.}$), 173.70 (COOH). MINOR (*trans* isomer): **^{1}H-NMR (270 MHz, D_2O) δ:** 2.50-2.60 (4H, m, 2 x CH_2), 2.85-3.05 (1H, m, CH ring), 3.60 (2H, d, *J*= 7.6 Hz, CH_2Br). **^{13}C-NMR (68 MHz, D_2O) δ:** 2.4 (CH_3CN), 30.58 (CH ring), 35.00 (CH_2 ring), 38.41 (CH_2Br), 55.16 ($C_{quat.}$), 173.83 (COOH). **IR (cm^{-1}) ν_{max} :** 1728. **MS: m/z (%):** (ES, pos) 208/210 (M^+, 100), 164 (45), 162 (44), 128 (40).

1-Amino-3-oxabicyclo[3.1.1]heptan-2-one 373

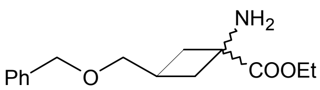
A mixture of the pure 1-amino-3-(bromomethyl)cyclobutanecarboxylic acid hydrobromide (5 mmol) was dissolved in acetonitrile (3% solution). 4 Equivalents of triethyl amine were added and the resulting suspension was heated under reflux for 2 days. After cooling, diethyl ether was added (half of the original amount of solvent) and the mixture was filtered. Evaporation of the solvent led to the isolation of 1-amino-3-oxabicyclo[3.1.1]heptan-2-one as an oil (yield = 5%). The solid residue on the filter contained the 2,4-methanoproline which was crystallised ($MeOH/H_2O$ 1/1) to give the pure 2,4-methanoproline in 50 % yield.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.04 (2H, br. s, NH_2), 2.11 (2H, dd (+ 2 sym side lines), *J*= 6.9 Hz, *J*= 2.6 Hz, (*J*= 9.9 Hz from centre of signal), $C\underline{H}_aH_bCH$), 2.29 (2H, ddd, *J*= 6.9 Hz, *J*= 6.9 Hz, *J*= 2.6 Hz, $CH_a\underline{H}_bCH$), 2.64 (1H, tt, *J*= 6.9 Hz, *J*= 1.7 Hz, CH), 4.43 (2H, d, *J*= 1.7 Hz, CH_2O). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.91 (CH), 37.79 (CH_2), 57.66 ($C_{quat.}$), 73.62 (CH_2O), 177.28 ($\underline{C}OOCH_2$). **IR (cm^{-1}) ν_{max} :** 1743. **MS: m/z (%):** (GC) 127 (M^+, 16), 96 (20), 82 (100), 69 (34), 42 (70).

Ethyl 1-amino-3-[(benzyloxy)methyl]cyclobutanecarboxylate 371

This compound was synthesised starting from 2.66 g (0.01 mmol) 2-[(benzyloxy)methyl]-5,7-diazaspiro[3.4]octane-6,8-dione which was first hydrolysed with NaOH as described above and subsequently treated with hydrochloric acid to get a mixture of 5 g of the diastereoisomers of 1-amino-3-[(benzyloxy)methyl]cyclobutanecarboxylic acid hydrochloride. This compound was further used in the reaction although it still contained a lot of inorganic salts. 50 ml of absolute ethanol was cooled to -15°C (in an ice bath containing NaCl) and 2.36 g of thionyl chloride (2 equiv.) were added. The solution was stirred at this temperature for 5 minutes and then all the white crystalline amino acid was added in one portion. The suspension was stirred another 15 minutes at -15°C and then allowed to warm to 0°C and stirred for 30 minutes at this temperature. The reaction was subsequently heated for 2 hours under reflux. The solution was filtered after cooling down and dichloromethane was added and washed with a saturated NH_4HCO_3 solution until basic. The organic layer was dried with $MgSO_4$ overnight. Filtration and evaporation of the solvent gave 2.2 g (82 %; 73/27) of the pure ethyl 1-amino-3-[(benzyloxy)methyl]cyclobutanecarboxylate as an oil.



MAJOR: **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 1.23-1.33 (3H, m, $COOCH_2C\underline{H}_3$), 1.86-1.93 (2H, m, CH_2 ring), 2.47-2.71 (3H, m, CH_2 ring + CH ring), 3.44-3.52 (2H, m, $OC\underline{H}_2CH$), 4.11-4.25 (2H, m, $OC\underline{H}_2CH_3$), 4.53 (2H, s, OCH_2Ph), 7.26-7.38 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.14 ($COOCH_2\underline{C}H_3$), 26.79 (CH ring), 37.83 (CH_2 ring), 55.18 ($C_{quat.}$ ring), 61.01 ($COO\underline{C}H_2CH_3$), 72.96 (OCH_2Ph), 74.03 ($O\underline{C}H_2CH$), 127.56 (CH), 128.26 (CH), 138.47 ($C_{quat.}$, Ph), 175.76 (C=O).

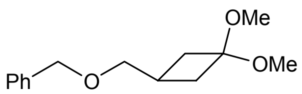
MINOR: **^{1}H-NMR (270 MHz, $CDCl_3$) δ:** 1.23-1.33 (3H, m, $COOCH_2C\underline{H}_3$), 1.99-2.11 (2H, m, CH_2 ring), 2.32-2.41 (2H, m, CH_2 ring), 2.76-2.87 (1H, m, CH ring), 3.44-3.52 (2H, m, $OC\underline{H}_2CH$), 4.11-4.25 (2H, m, $COOC\underline{H}_2CH_3$), 4.51 (2H, s, OCH_2Ph), 7.26-7.38 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.14 ($COOCH_2\underline{C}H_3$), 27.89 (CH ring), 35.79 (CH_2 ring), 55.36 ($C_{quat.}$, ring), 61.01 ($COO\underline{C}H_2CH_3$), 72.81 (OCH_2Ph), 73.98 ($O\underline{C}H_2CH$), 127.51 (CH), 128.26 (CH), 138.56 ($C_{quat.}$, Ph), 175.76 (C=O). **IR (cm^{-1}) ν_{max} :** 1725. **MS: m/z (%):** (direct inlet) 263 (M^+, 5), 234 (9), 190 (18), 115 (100), 91 (85), 71 (64).

6.11. Entry to 3-halomethyl cyclobutanones

6.11.1. From 3-[(benzyloxy)methyl]cyclobutanone

3-Benzyloxymethyl-1,1-dimethoxycyclobutane 386

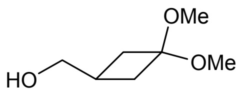
To a solution of 10 g (52.6 mmol) 3-(benzyloxymethyl)cyclobutanone in 150 ml of MeOH, 1g (0.1 equiv.) p-toluenesulfonic acid was added and the resulting solution was refluxed for 5 h, after which, 100 ml of water and 100 ml of dichloromethane was added. The organic layer was washed with water (2 x 50 ml). Subsequently the combined water layers were extracted with dichloromethane (1 x 100 ml). After drying the organic phases with $MgSO_4$, the suspension was filtered and the filtrate was evaporated. 11.69 g (yield = 94%) Of pure 3-benzyloxymethyl-1,1-dimethoxycyclobutane was obtained as an oil.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.82-1.88 (2H, m, CH_2 ring), 2.24-2.34 (3H, m, CH_2 ring, CH), 3.11 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 3.48 (2H, d, *J*= 6.6 Hz, $OC\underline{H}_2CH$), 4.52 (2H, s, OCH_2Ph), 7.29-7.38 (5H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 24.78 (CH), 34.68 (CH_2 ring), 47.98 (OCH_3), 48.23 (OCH_3), 72.87 (OCH_2), 74.37 (OCH_2), 100.83 ($C_{quat.}$ ring), 127.47 (CH), 127.55 (CH), 128.32 (CH), 138.69 ($C_{quat.}$, Ph). **IR (cm^{-1}) ν_{max} :** 1600, 1499, 1453, 1156. **MS: m/z (%):** (direct inlet) no M^+, 205 (8), 204 (8), 189 (8), 176 (6), 145 (5), 131 (7), 97 (22), 91 (61), 88 (100), 83 (25).

3-Hydroxymethyl-1,1-dimethoxycyclobutane 387

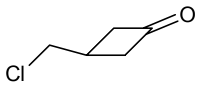
1g of 3-benzyloxymethyl-1,1-dimethoxycyclobutane was dissolved in 10 ml of MeOH in the presence of 0.45 g (0.1 equiv.) Pd-C and was stirred under a H_2-atmosphere (5 bar of H_2-pressure) for 10 hours. The suspension was filtered over celite and the filtrate was evaporated under reduced pressure. 0.46 g of pure 3-hydroxymethyl-1,1-dimethoxycyclobutane (yield = 74 %) was obtained as an oil.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.88-1.91 (2H, m, CH_2 ring), 2.27-2.29 (3H, m, CH_2 ring + CH), 3.14 (3H, s, OC$\underline{H}_3$), 3.16 (3H, s, OC$\underline{H}_3$), 3.64 -3.65 (2H, m, CH_2OH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 26.26 (CH), 33.62 (CH_2), 47.51 (OCH_3), 47.57 (OCH_3), 47.78 (OCH_3), 47.85 (OCH_3), 65.75 (CH_2OH), 100.32 ($C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 3406, 1155. **MS: m/z (%):** (GC) no M^+, 115 (24), 114 (16), 89 (9), 88 (100), 83 (71), 58 (77), 43 (92).

3-(Chloromethyl)cyclobutanone 37

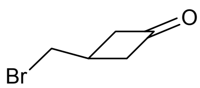
0.5 g of 3-(benzyloxymethyl)cyclobutanone (2.6 mmol) was dissolved in 10 ml of HCl (12N solution) and 3 g of $ZnCl_2$ was added. The resulting suspension was heated under reflux overnight. The reaction mixture was cooled, 20 ml of water was added and the mixture was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried with $MgSO_4$. Filtration and evaporation of the solvent led to the isolation of 0.44 g of crude 3-(chloromethyl)cyclobutanone. This product was purified by means of flash chromatography and 0.15 g of 3-(chloromethyl)cyclobutanone was obtained (48 %).



For spectral data see preparation of 3-(chloromethyl)cyclobutanone by [2+2]-cycloaddition on allylchloride page 147.

3-(Bromomethyl)cyclobutanone 390

A solution of 5.0 g (26.3 mmol) of cyclobutanone in 50 ml of concentrated hydrobromic acid (48 % solution in water) was refluxed for 7h. Subsequently, 100 ml of dichloromethane was added and the reaction mixture was washed with 100 ml of water and 100 ml of a saturated $NaHCO_3$-solution. The organic phase was dried with $MgSO_4$. After filtration and evaporation of the solvent, the brown liquid was purified by flash chromatography (Hex/EtOAc 80/20; R_f = 0.25) and 2.3 g (14.1 mmol, 54%) of 3-(bromomethyl)cyclobutanone was obtained as a clear brown oil.

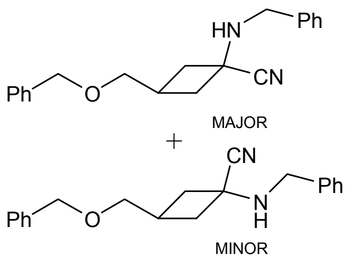


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.86-2.97 (3H, m, CH_2 ring + CH), 3.14-3.27 (2H, m, CH_2 ring), 3.64 (2H, d, J = 6.3 Hz, CH_2Br). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 26.4 (CH), 37.9 (CH_2Br), 51.9 (CH_2 ring), 205.1 (C=O). **IR (cm^{-1}) ν_{max} :** 1788. **MS: m/z (%):** 165/163 (M^+, 2), 84 (63), 55 (100). **Chromatography**: Hex/EtOAc 80/20 R_f= 0.25.

6.11.1.1. Synthesis of 1-(benzylamino)-3-[(benzyloxy)methyl]cyclobutanecarbonitrile

1-(Benzylamino)-3-[(benzyloxy)methyl]cyclobutanecarbonitrile 377/378

0.5 g of 3-(benzyloxymethyl)cyclobutanone was dissolved in 4 ml of dry MeOH and 0.28 g (1 equiv.) of benzylamine was added under a N_2-atmosphere. The resulting solution was stirred at room temperature for two hours after which it was cooled to 0°C. Then, 0.53 g of trimethylsilyl cyanide (2 equiv.) was added and allowed to warm to room temperature and was further stirred for 48 hours. After this time the solvent was removed under reduced pressure and 0.80 g pure 1-(benzylamino)-3-[(benzyloxy)methyl]cyclobutanecarbonitrile was obtained as an oil (yield = 99 %).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.99-2.09 (2H, m, C$\underline{H}_a$H$_b$ 4 ring), 2.61-2.77 (3H, m, CH$_a\underline{H}_b$ + CH), 3.49 (2H, d, *J*= 5.6 Hz, OC$\underline{H}_2$CH), 3.77 (2H, s, NHC$\underline{H}_2$Ph), 4.50 (2H, s, OCH_2Ph), 7.24-7.35 (10H, m, Ph); MINOR: 2.12-2.42 (4H, m, 2x CH_2 ring), 2.79-2.91 (1H, m, CH), 3.51 (2H, d, *J*= 6.3 Hz, OC$\underline{H}_2$CH), 3.81 (2H, s, NHC$\underline{H}_2$Ph), 4.53 (2H, s, OC$\underline{H}_2$Ph), 7.24-7.35 (10H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 28.19 (CH ring), 36.26 (CH_2, ring), 48.88 ($NHCH_2Ph$), 51.14 ($C_{quat.}$), 72.74 (OCH_2), 72.90 (OCH_2), 122.32 (CN), 127.28 (CH), 127.51 (CH), 128.34 (CH), 138.17 ($C_{quat.}$, Ph), 138.78 ($C_{quat.}$, Ph); MINOR: 30.10 (CH), 35.26 (CH_2, ring), 49.02 (NH$\underline{C}$H$_2$Ph), 50.10 ($C_{quat.}$), 72.90 (OCH_2), 72.96 (OCH_2), 121.62 ($\underline{C}$N), 126.92 (CH), 127.58 (CH), 128.26 (CH), 138.78 ($C_{quat.}$, Ph), 138.92 ($C_{quat.}$, Ph). **IR (cm^{-1}) ν_{max} :** 2218. **MS: m/z (%):** (ES, Pos) 307 (M^++H, 100), 280 (38), 190 (35), 91 (10).

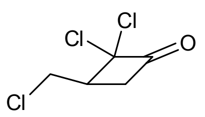
6.11.2. By [2+2]-cycloaddition on allylchloride

3-(Chloromethyl)-2,2-dichlorocyclobutanone 381

Activation of Zinc:

In a 2-necked flask of 500 ml, 50 g (760 mmol) of zinc in 200 ml of distilled water is stirred vigorously for 15 min while nitrogen gas is bubbled through. After this period 3.75 g of copper(II)sulphate (23 mmol) was added at once, and the resulting suspension was stirred during another 45 minutes while the bubbling of nitrogen gas was continued. The Zn-Cu couple was filtered under a nitrogen atmosphere and washed with respectively 500 ml of degassed water and 500 ml of degassed acetone. The black powder was transferred to a flask of 100 ml and dried at high vacuum (0.2 mmHg) for 2 hours because the Zn-Cu should be completely dry prior to use. When the vacuum was disconnected, the flask is flushed with nitrogen gas and the Zn-Cu is kept under a nitrogen atmosphere in a sealed flask (stored at room temperature).

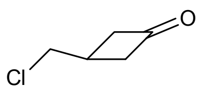
In an oven-dried 3-necked flask of 500 ml, a solution of 26.7 g of allyl chloride and 14 g of an activated Zn-Cu couple in 180 ml of dry ether was cooled to 0°C under a nitrogen atmosphere. Over a period of half an hour, a solution of 19.5 ml of trichloroacetyl chloride and 25 ml of $POCl_3$ in 140 ml of dry ether were added. After refluxing the reaction mixture for one day (under a N_2-atmosphere), the solution was filtered over celite and washed with ether. The filtrate was evaporated to 200 ml. This solution was extracted with 3 x 150 ml of petroleum ether. The clear yellow upper solution was decanted from the brown residue into a separatory funnel of 1000 ml. The organic layer was washed with 3x100 ml of water and 1x100 ml of a saturated NaCl-solution. After drying the organic layer with $MgSO_4$, evaporation of the solvent led to 11.96 g (63.76 mmol) of 3-(chloromethyl)-2,2-dichlorocyclobutanone. (bp 45°C/0.5mm Hg; clear liquid: crystallises at -18°C but melts at room temperature; yield = 37%). (1. If, after one day of reflux, the Zn is no more in suspension, the yield will be low indicating that some traces of water were present; 2. it is better to remove first the two geminal chloride atoms on the crude mixture of this reaction before purifying it).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.21 (1H, dd, J = 16.8 Hz, J = 8.2 Hz, C<u>H</u>$_2$C=O), 3.3-3.4 (1H, m, CH), 3.52 (1H, dd, J = 16.8 Hz, J = 9.2 Hz, C<u>H</u>$_2$C=O), 3.77 (1H, dd, J = 11.6 Hz, J = 6.9 Hz, CH_2Cl), 3.95 (1H, dd, J = 11.6 Hz, J = 7.2 Hz, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 42.93 (CH_2Cl), 46.77 (<u>C</u>H$_2$C=O), 46.85 (CH), 86.86 ($C_{quat.}$, <u>C</u>Cl$_2$, 191.08 (C=O); IR (NaCl): 1810 cm^{-1} (C=O). **MS: m/z (%):** 186/188/190/192 (M^+, 1), 151/153/155 (8), 146 (26), 144 (27), 111 (65), 109 (100), 87 (13), 73 (9), 51 (14). **bp.**= 45°C/0.5 mmHg.

3-(Chloromethyl)cyclobutanone 37

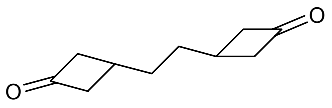
(See also ref. [37]). A solution of 23.77 g of 3-(chloromethyl)-2,2-dichlorocyclobutanone in 20 ml of acetic acid (glacial) was slowly added to a vigorously stirred solution of 54 g of zinc in 200 ml of glacial acetic acid. During the addition, the solution starts to reflux and refluxing is maintained for 4 additional hours. After cooling, the mixture is filtered over celite and washed with dichloromethane. The filtrate was poured into a separatory funnel of 1000 ml containing 200 ml of dichloromethane. The solution was washed with 100 ml of water and afterwards with a saturated $NaHCO_3$ solution until basic. The organic phase was dried with $MgSO_4$, filtered and evaporated. Distillation of the crude product leads to the isolation of 12.76 g of 3-(chloromethyl)cyclobutanone as a clear oil (yield 85%, bp 65 °C/4.5 mmHg).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.80-2.90 (1H, m, CH), 2.92-2.99 (2H, m, CH_2), 3.16-3.22 (2H, m, CH_2), 3.75 (2H, d, J= 6.6 Hz, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 26.08 (CH), 48.29 (CH_2Cl), 50.85 (CH_2), 205.11 (C=O). **IR (cm^{-1}) ν_{max} :** 1785. **MS: m/z (%):** 159/161 (M+, 4), 144/146 (2), 108 (4), 83 (58), 82 (10), 68 (6), 55 (18), 43 (38), 41 (100), 40 (28). **Bp**.= 70-75°C/ 4.5 mmHg.

3-[2-(3-oxocyclobutyl)ethyl]cyclobutanone 385

During the distillation of the 3-(chloromethyl)cyclobutanone some residue was formed. After purification by means of bulb to bulb distillation of this residue the main compound was identified as 3-[2-(3-oxocyclobutyl)ethyl]cyclobutanone and was isolated as an oil with a yield of 3 %.



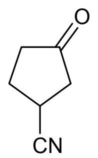
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.64 (4H, dt, *J*= 7.3 Hz, *J*= 3.6 Hz, C<u>H</u>$_2$C<u>H</u>$_2$), 2.33-2.42 (2H, m, CH ring), 2.63-2.75 (4H, m, CH_2 ring), 3.12-3.24 (4H, m, CH_2 ring). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 23.61 (CH ring), 34.88 (<u>C</u>H$_2$<u>C</u>H$_2$), 52.49 (CH_2 ring x 4), 207.96 (C=O). **IR (cm^{-1}) ν_{max} :** 1776 (C=O). **MS: m/z (%):** (GC) no M^+, 138 (20), 124 (9), 112 (18), 96 (24), 95 (14), 83 (22), 82 (22), 81 (31), 68 (58), 67 (100), 55 (58). **Chromatography**: strip column with CH_2Cl_2 than strip with EtOAc.

6.12. Reactions with 3-(chloromethyl)cyclobutanone

6.12.1. Ring expansion of 3-(chloromethyl)cyclobutanone

3-Cyanocyclopentanone 398

This compound was formed as result of an unwanted side reaction. 0.3 g of 3-(chloromethyl)cyclobutanone was dissolved in 10 ml of MeOH. A mixture of 0.16 g ammonium chloride (1.2 equiv.) and 0.2 g potassium cyanide (1.2 equiv.) was dissolved in 10 ml of water and added to the mixture described above. The resulting solution was heated at 65°C overnight. After performing an extraction, with dichloromethane and drying the organic phase with $MgSO_4$, filtration and evaporation of the solvent gave a mixture that was purified by column chromatography. 0.09 g of 3-cyanocyclopentanone (yield = 33%) was obtained as an oil together with 0.1 g of starting material.

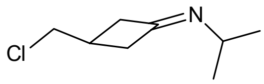


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.20-2.36 (2H, m, CH_2), 2.38-2.68 (4H, m, 2 x CH_2), 3.17-3.26 (1H, m, CHCN). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 25.14 (CH), 26.94 (CH_2), 36.35 (CH_2), 41.03 (CH_2), 120.72 (CN), 212.83 (C=O). **IR (cm^{-1}) ν_{max} :** 2237, 1747. **MS: m/z (%):** 110 (M^++1, 91), 82 (93), 55 (80), 53 (100). **Chromatography:** EtOAc/Hex 75/25 R_f = 0.44.

6.12.2. Synthesis of N-[3-(chloromethyl)-1-cyclobutylidene]amines

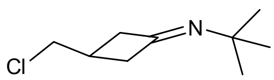
To a solution of 2.2 g (18.6 mmol) of 3-(chloromethyl)cyclobutanone in 25 ml of dry ether, 74.4 mmol (4 equiv.) of primary amine was added, followed by dropwise addition of 0.6 equiv. of titanium(IV) chloride in 5 ml of pentane at 0 °C. The reaction mixture was stirred overnight at room temperature, filtered, poured into 20 ml of sodium hydroxide (1N), and extracted with diethyl ether. After drying ($MgSO_4$), filtration and evaporation of the solvent, δ-chloroimines were obtained as oils with a sufficient purity for further use (> 95 % purity). The benzyl derivative was prepared using only 3 equiv. of benzylamine and 0.5 equiv. titanium(IV) chloride. The reaction was stirred for 4h at 0°C followed by the described workup.

N-[3-(Chloromethyl)-1-cyclobutylidene]isopropylamine 38a



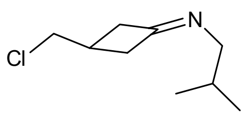
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.11 (6H, d, *J*= 6.3 Hz, $NCH(C\underline{H}_3)_2$), 2.64-2.76 (3H, m, CH_2 ring, CH ring), 2.99-3.09 (2H, m, CH_2 ring), 3.42 (1H, sept., *J*= 6.3 Hz, $NC\underline{H}(CH_3)_2$), 3.64-3.67 (2H, m, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 22.88 ($NCH(\underline{C}H_3)_2$), 28.63 (CH ring), 37.32 (CH_2 ring), 40.72 (CH_2 ring), 48.12 (CH_2Cl), 51.25 ($N\underline{C}H(CH_3)_2$), 163.45 (C=N). **IR (cm^{-1}) ν_{max} :** 1712. **MS: m/z (%):** (GC) 159/161 (M^+, 4), 83 (58), 82 (10), 55 (18), 43 (38), 41 (100). Yield = 80 %.

N-[3-(Chloromethyl)-1-cyclobutylidene]-t-butylamine 38b



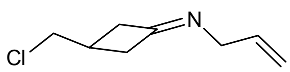
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.23 (9H, s, t-Bu), 2.6-2.8 (2H, m, CH_2 ring), 2.8-2.9 (1H, m, CH ring), 3.0-3.1 (1H, m, $C\underline{H}_aH_b$ ring), 3.15-3.30 (1H, m, $CH_a\underline{H}_b$ ring), 3.63-3.66 (2H, m, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 29.67 (CH ring), 29.97 (t-Bu), 42.42 (CH_2), 43.32 (CH_2), 48.93 (CH_2Cl), 56.49 ($C_{quat.}$), 163.27 (C=N). **IR (cm^{-1}) ν_{max} :** 1710. **MS: m/z (%):** (GC) 173/175 (M^+, 1), 158 (1), 122 (2), 97 (8), 82 (5), 57 (100). Yield = 76 %.

N-[3-(Chloromethyl)-1-cyclobutylidene]isobutylamine 38c



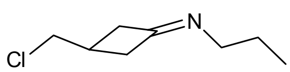
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.92 (6H, d, *J*= 6.6 Hz, CH_3), 1.90 (1H, sept, *J*= 6.6 Hz, $NCH_2C\underline{H}(CH_3)_2$), 2.60-2.80 (3H, m, CH_2 ring + CH), 3.0-3.18 (4H, m, $NC\underline{H}_2CH(CH_3)_2$ + CH_2 ring), 3.64-3.67 (2H, m, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 20.66 (CH_3), 29.22 (CH), 29.38 (CH), 38.60 (CH_2 ring), 41.46 (CH_2 ring), 48.84 (CH_2Cl), 60.09 (NCH_2), 166.61 (C=N). **IR (cm^{-1}) ν_{max} :** 1717. **MS: m/z (%):** 173/175 (M^+, 4), 97 (57), 94 (50), 57 (100). Yield = 77 %.

N-[3-(Chloromethyl)-1-cyclobutylidene]allylamine 38d



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.61-2.80 (3H, m, CH_2 ring)), 2.98-3.25 (2H, m, CH_2 ring), 3.63-3.66 (2H, m, CH_2 Cl), 3.86 (2H, dd, *J*= 4.3 Hz, *J*= 1.3 Hz, $NC\underline{H}_2CH{=}CH_2$), 5.03 (1H, dq, *J*= 10.4 Hz, *J*= 1.7 Hz, $NCH_2CH{=}C\underline{H}_aH_b$), 5.16 (1H, dq, *J*= 17.3 Hz, *J*= 1.7 Hz, $NCH_2CH{=}CH_a\underline{H}_b$), 5.96 (1H, ddt, *J*= 17.2 Hz, *J*= 10.2 Hz, *J*= 5.6 Hz, $NCH_2C\underline{H}{=}CH_2$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 29.15 (CH ring), 38.42 (CH_2 ring), 41.49 (CH_2 ring), 48.73 (CH_2Cl), 54.68 ($N\underline{C}H_2CH{=}CH_2$), 115.43 ($NCH_2CH{=}\underline{C}H_2$), 135.51 ($NCH_2\underline{C}H{=}CH_2$), 168.3 (C=N). **IR ($cm^{-1}$) ν_{max} :** 1714. **MS: m/z (%):** 157/159 (M^+, 2), 120 (2), 81 (100), 53 (5). Yield = 89 %.

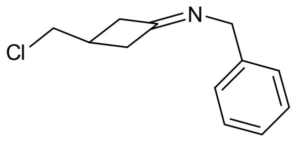
N-[3-(Chloromethyl)-1-cyclobutylidene]propylamine 38e



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J*= 7.3 Hz, $NCH_2CH_2C\underline{H}_3$), 1.62 (2H, sex, *J*= 7.3 Hz, $NCH_2C\underline{H}_2CH_3$), 2.61-2.79 (3H, m, CH_2 ring + CH), 2.98-3.12 (2H, m, CH_2 ring), 3.17 (2H, t, *J*= 7.1 Hz, $NC\underline{H}_2CH_2CH_3$), 3.64-3.66 (2H, m, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 11.95 ($NCH_2CH_2\underline{C}H_3$), 23.68

($NCH_2CH_2CH_3$), 29.20 (CH), 38.42 (CH_2 ring), 41.38 (CH_2 ring), 48.84 (CH_2Cl), 53.87 (NCH_2), 166.95 (C=N). **IR (cm^{-1}) ν_{max} :** 1714. **MS: m/z (%):** 159/161 (M^+, 7), 123 (5), 94 (17), 83 (100), 68 (13), 55 (19), 41 (88). Yield = 95 %.

N-[3-(Chloromethyl)-1-cyclobutylidene]benzylamine 38f

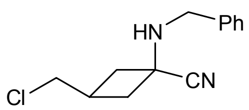


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2,70-2.84 (3H, m, CH ring + CH_2 ring), 3.06-3.19 (2H, m, CH_2 ring), 3.63-3.67 (2H, m, CH_2Cl), 4.42 (2H, s, CH_2Ph), 7.21-7.36 (5H, m, CH, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 29.16 (CH ring), 38.67 (CH_2 ring), 41.55 (CH_2 ring), 48.73 (CH_2Cl), 56.21 (NCH_2Ph), 126.84 (CH), 127.87 (CH), 128.50 (CH), 139.39 ($C_{quat.}$, Ph), 168.34 (C=N). **IR (cm^{-1}) ν_{max} :** 1713. **MS: m/z (%):** (GC) 207/209 (M^+, 3), 172 (2), 158 (2), 131 (13), 92 (9), 91 (100), 65 (9). Yield = 89 %.

6.12.3. Synthesis of 3-(chloromethyl)-1-(alkylamino)cyclobutane carbonitrile

3-(Chloromethyl)-1-(benzylamino)cyclobutane carbonitrile 417a, 418a

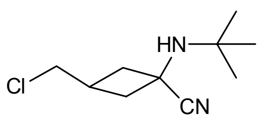
This compound was prepared using the same procedure as the first method to prepare 1-amino-3-(chloromethyl)cyclobutanecarbonitrile except that, instead of using ammonium formate, 1 equiv. of benzyl amine was used. After removal of the solvent no purification was necessary and the product was obtained as an oil (yield = 99%; 76/24).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR, *MINOR*, not assigned: 2.01-2.10 (2H, m, CH_2 ring), 2.18 (1H, br. s, NH), *2.24-2.44* (4H, m, CH_2 ring), 2.63-2.71 (2H, m, CH_2 ring), 2.70-2.86 (1H, m, CH ring), *2.87-3.03* (1H, m, CH ring), *3.62* (2H, d, *J*= 6.9 Hz, CH_2Cl), 3.63 (2H, d, *J*= 6.6 Hz, CH_2Cl), 3.79 (2H, s, NCH_2Ph), *3.82* (2H, s, NCH_2Ph), 7.24-7.34 (5H, m, Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 30.12 (CH ring), *31.90* (CH ring), *35.76* (CH_2 ring), 36.70 (CH_2 ring), 47.96 (CH_2Cl), 48.47 (CH_2Ph), *48.63* (CH_2Cl), *48.90* (NCH_2Ph), 50.05 ($C_{quat.}$), *50.32* ($C_{quat.}$), *120.79* (CN), 121.44 (CN), 127.87 (CH), 127.96 (CH), 128.09 (CH), 138.22 ($C_{quat.}$, Ph), 138.42 ($C_{quat.}$, Ph). **IR (cm^{-1}) ν_{max} :** 2220. **MS: m/z (%):** MAJOR: no M^+, 207/209 (2), 171 (7), 131 (13), 91 (100), 65 (9). MINOR: no M^+, 207/209 (3), 171 (7), 131 (12), 91 (100), 65 (9).

1-(t-butylamino)-3-(chloromethyl)cyclobutane carbonitrile 417b, 418b

Analogue procedure was used as for the synthesis of 3-(chloromethyl)-1-(benzylamino)cyclobutane carbonitrile but use t-butyl amine instead of benzyl amine (yield = 98 %; 71/29). The product was isolated as an oil.



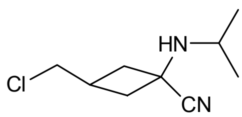
^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR, *minor*, not assigned: 1.23 (9H, s, t-Bu), *1.25* (9H, s, t-Bu), 2.00-2.10 (2H, m, CH_2 ring), *2.34-2.51* (4H, m, 2 x CH_2 ring), 2.69-2.77 (2H, m, CH_2 ring), 2.72-2.86 (1H, m, CH ring major and minor), 3.58 (2H, d, *J*= 5.9 Hz, CH_2Cl), *3.69* (2H, d, *J*= 7.26 Hz,

CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 30.40 (t-Bu), 30.58 (CH ring), 41.33 (CH_2 ring), 46.92 ($C_{quat.}$), 48.12 (CH_2Cl), 52.40 ($C_{quat.}$), 124.58 (CN); MINOR: 30.49 (t-Bu), 31.55 (CH ring), 39.89 (CH_2 ring), 45.86 ($C_{quat.}$), 48.34 (CH_2Cl), 50.84 ($C_{quat.}$), 124.58 (CN). **IR (cm^{-1}) ν_{max} :** 2217 (CN). **MS: m/z (%):** (GC) no M^+, 173/175 (4), 158/160 (4), 97 (16), 57 (100). **Chromatography**: Hex/EtOAc 65/35 R_f= 0.34.

3-(Chloromethyl)-1-(isopropylamino)cyclobutane carbonitrile 417c, 418c

First procedure: Hydrogen cyanide gas was generated by addition of a concentrated hydrochloric acid solution to potassium cyanide (2.4 g, 5 equiv.) in a well-ventilated hood (caution !). The gas was passed through a tube containing $CaCl_2$ and an empty wash bottle and was then bubbled into a solution of 1.18 g of imine (7.4 mmol) dissolved in 50 ml of dry ether. The reaction mixture was stirred at 0°C for 5 h while a nitrogen flow was used as HCN gas carrier through the set-up. The exhaust of gas was passed again through an empty wash bottle and twice through a 6N solution of sodium hydroxide (wash bottle) to trap the excess of hydrogen cyanide gas. After 5h, the ether was evaporated and 1.35 g of pure 3-(chloromethyl)-1-[isopropylamino]cyclobutane carbonitrile was obtained as a mixture of cis/trans isomers (3/1; clear oil; yield = 98 %).

Second procedure: an analogous procedure as for the synthesis 3-(chloromethyl)-1-(benzylamino)cyclobutane carbonitrile but isopropyl amine was used instead of benzyl amine (yield = 99 %; 76/24).

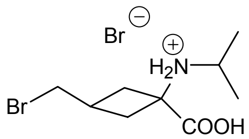


^{1}H-NMR (270 MHz, $CDCl_3$) δ: <u>MAJOR</u>, *minor*, not assigned: <u>1.08</u> (6H, d, J = 6.3 Hz, $NCH(C\underline{H}_3)_2$), *1.11* (6H, d, J = 6.3 Hz, $NCH(C\underline{H}_3)_2$), <u>2.01-2.09</u> (2H, m, CH_2 ring), *2.29-2.42* (4H, m, 2 x CH_2 ring), 2.67-2.91 (3H, m, CH_2 + CH ring), 3.13 (1H, sept, J = 6.3 Hz, $NC\underline{H}(CH_3)_2$), <u>3.59</u> (2H, d, J = 6.3 Hz, CH_2Cl), *3.65* (2H, d, J = 6.3 Hz, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 23.40 ($NCH(\underline{C}H_3)_2$), 30.53 (CH ring), 39.33 (CH_2 ring), 46.85 ($N\underline{C}H(CH_3)_2$), 48.21 (CH_2Cl), 49.70 ($C_{quat.}$), 122.17 (CN); MINOR: 23.68 ($NCH(\underline{C}H_3)_2$), 31.68 (CH ring), 37.90 (CH_2 ring), 47.01 ($N\underline{C}H(CH_3)_2$), 48.37 (CH_2Cl), 50.73 ($C_{quat.}$), 121.92 (CN). **IR (cm^{-1}) ν_{max} :** 2219. **MS: m/z (%):** (cis, the trans derivative ring closes during GC-analysis): no M^+, 173/171 (14), 95 (51), 83 (78), 43 (55), 41 (100). **Chromatography**: Hex/EtOAc 70/30 R_f= 0.21 (visible with $KMnO_4$).

6.12.3.1. Synthesis of 3-(bromomethyl)-1-(isopropylamino)cyclobutane carboxylic acid hydrobromide

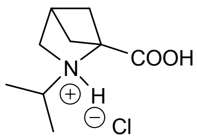
3-(Bromomethyl)-1-(isopropylamino)cyclobutane carboxylic acid hydrobromide 402, 403

A solution of 0.52 g (12.8 mmol) of 3-(chloromethyl)-1-(isopropylamino)cyclobutane carbonitrile in 13 ml of concentrated hydrobromic acid (48% solution in water) was refluxed overnight. After cooling of the reaction mixture, 10 ml of distilled water was added and the mixture was filtered over a paper filter and washed with water. Evaporation of the solvent and recrystallisation from a water methanol mixture (1/1) gave 0.7 g (2.1 mmol, 76 %) of the amino acid as a white powder.



^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.23 (6H, d, *J* = 6.6 Hz, $NCH(C\underline{H}_3)_2$), 2.00 ($C\underline{H}_3CN$), 2.25-2.34 (2H, m, CH_2 ring), 2.67-2.77 (2H, m, CH_2 ring), 2.85 (1H, sept, *J* = 7.6 Hz, CH ring), 3.49 (2H, d, 6.6 Hz, CH_2Br), 3.54 (1H, sept, *J* = 6.2 Hz, $NC\underline{H}(CH_3)_2$). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 20.34 (CH_3), 31.37 (CH ring), 36.44 (2 x CH_2 ring), 38.32 (CH_2Br), 51.24 ($N\underline{C}H(CH_3)_2$), 58.54 ($C_{quat.}$, ring), 173.65 (COOH). **IR (cm^{-1}) ν_{max} :** 1737. **MS: m/z (%):** (methyl ester, after treatment with diazomethane) 263/265 (M^+, 2), 248/250 (2), 204/206 (26), 143 (44), 128 (100), 82 (22).

Synthesis of 2-(isopropyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride 404



To a solution of 0.11 g of sodium hydroxide in 5 ml of distilled water, 0.3 g (0.91 mmol) of 3-(bromomethyl)-1-(isopropylamino)cyclobutane carboxylic acid hydrobromide was added and the mixture was heated under reflux. After 1.5 h the reaction mixture was evaporated and 5 ml of 6N hydrogen chloride solution was added. After evaporation of the solution under vacuum, the obtained crystals were extracted with acetone and subsequently recrystallised from acetone giving 88 mg (0.44 mmol) of 2-(isopropyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride (yield 48 %). For the spectral data see page 155.

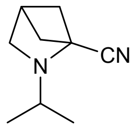
6.12.4. Synthesis of 2-alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitriles

To a solution of 16.6 mmol N-[3-(chloromethyl)-1-cyclobutylidene]alkylamine in 30 ml of dry methanol, 3 equiv. of acetone cyanohydrine were added and the reaction mixture was refluxed under a nitrogen atmosphere for 5 days. Purification can be performed by two means. The first way is by flash chromatography. After removal of the solvent (MeOH) under vacuum, 30 ml of dichloromethane is added together with 3 or 4 grammes of silica and the solvent was again evaporated. The product was then purified by flash chromatography which has the disadvantage of being time consuming and leading to a lower yield. The second way is more convenient and consists of an acid/base extraction. After removing the solvent under vacuum, 20 ml of a 2N HCl solution was added. The solution was extracted with diethyl ether to remove the excess of acetone cyanohydrine (3 x 40 ml). Afterwards a concentrated K_2CO_3 solution was added to the water layer until basic, followed by an extraction of the water layer with dichloromethane (3 x 50 ml). After drying the organic layer with $MgSO_4$ and filtration, evaporation of the solvent led to the end products as oils with a significantly higher yield.

2-isopropyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile 407a

Yield after chromatography = 50 %

Yield after acid/base extraction = 68 %

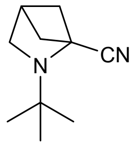


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.19 (6H, d, J= 6.6 Hz, CH$_3$), 1.88-1.9 (2H, m, CH$_2$ ring), 2.04-2.11 (2H, m, CH$_2$ ring), 2.72 (1H, t, J= 3.0 Hz, CH ring), 2.83 (2H, s, NCH$_2$), 3.12 (1H, sept, J= 6.3 Hz, NC<u>H</u>(CH$_3$)$_2$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 21.29 (CH$_3$), 37.77 (CH ring), 43.34 (CH$_2$ ring), 51.39 (NCH$_2$), 52.11 (N<u>C</u>H(CH$_3$)$_2$), 57.07 (C$_{quat.}$), 118.76 (CN). **IR (cm^{-1}) ν$_{max}$:** 2239. **MS: m/z (%):** 150 (M$^+$, 94), 135 (100), 107 (74), 81 (79), 68 (100). **Chromatography**: Hex/EtOAc 60/40 R$_f$= 0.16.

2-(t-butyl)-2-azabicyclo[2.1.1]hexane-1-carbonitrile 407b

Yield after chromatography = 40 %

Yield after acid/base extraction = 50 %

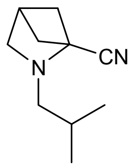


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.26 (9H, s, t-Bu), 1.93 (2H, dd (+ 2 sym. side lines), J= 4.3 Hz, J= 1.7 Hz, (J= 11.6 Hz from centre of signal), CH$_2$ ring), 2.05-2.10 (2H, m, CH$_2$ ring), 2.67-2.69 (1H, m, CH ring), 2.92 (2H, br. s, NCH$_2$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 28.18 (CH$_3$, t-Bu), 36.93 (CH ring), 44.96 (CH$_2$ ring), 49.56 (NCH$_2$), 55.08 (C$_{quat.}$ ring + C$_{quat.}$ t-Bu), 119.84 (CN). **IR (cm^{-1}) ν$_{max}$:** 2236. **MS: m/z (%):** 164 (M$^+$, 10), 149 (17), 108 (36), 93 (31), 82 (47), 57 (100). **Chromatography**: Hex/EtOAc 65/35 R$_f$= 0.22 (visible with KMnO$_4$).

2-(isobutyl)-2-azabicyclo[2.1.1]hexane-1-carbonitrilen 407c

Yield after chromatography = 56 %

Yield after acid/base extraction = 74 %

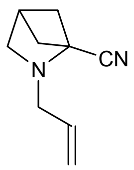


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 0.97 (6H, d, J= 6.6 Hz, CH$_3$), 1.74 (1H, sept, J= 6.6 Hz, NCH$_2$C<u>H</u>(CH$_3$)$_2$), 1.86 (2H, dd (+ 2 sym. side lines), J= 4.5 Hz, J= 1.8 Hz, (J= 11.4 Hz from centre of signal), CH$_2$ ring), 1.9-2.07 (2H, m, CH$_2$ ring), 2.46 (2H, d, J= 7.3 Hz, NC<u>H$_2$</u>CH(CH$_3$)$_2$), 2.73 (3H, br. s, NCH$_2$ ring + CH ring). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 20.83 (CH$_3$), 27.96 (NCH$_2$<u>C</u>H(CH$_3$)$_2$), 38.99 (CH ring), 42.25 (CH$_2$ ring), 56.12 (NCH$_2$ ring), 59.84 (C$_{quat.}$), 62.16 (N<u>C</u>H$_2$CH(CH$_3$)$_2$), 118.17 (CN). **IR (cm^{-1}) ν$_{max}$:** 2241. **MS: m/z (%):** 164 (M$^+$, 44), 121 (100), 109 (53), 67 (46), 41 (49).

2-allyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile 407d

Yield after chromatography = 55 %

Yield after acid/base extraction = 78 %

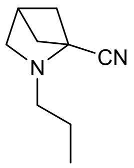


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.89 (2H, dd (+ 2 sym. side lines), J= 4.5 Hz, J= 1.8 Hz, (J= 11.5 Hz from centre of signal), CH$_2$ ring), 2.09-2.12 (2H, m, CH$_2$ ring), 2.74 (2H, br. s, NCH$_2$ ring), 2.75 (1H, t, J= 0.7 Hz, CH ring), 3.38 (2H, dt, J= 5.9 Hz, J= 1.3 Hz, N$C\underline{H}_2$CH=CH_2), 5.18 (1H, ddt, *J*= 10,2 Hz, *J*= 1.7 Hz, *J*= 1.3 Hz, $NCH_2CH=C\underline{H}_aH_b$), 5.28 (1H, ddt, *J*= 17.2 Hz, *J*= 1.7 Hz, *J*= 1.3 Hz, $NCH_2CH=CH_a\underline{H}_b$), 5.93 (1H, ddt, *J*= 17.2 Hz, *J*= 10.2 Hz, *J*= 5.9 Hz, $NCH_2C\underline{H}=CH_2$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 38.98 (CH ring), 42.07 (CH_2 ring), 54.70 (NCH_2 ring), 56.41 ($N\underline{C}H_2CH=CH_2$), 59.19 ($C_{quat.}$), 117.52 ($NCH_2CH=\underline{C}H_2$), 117.66 (CN), 134.84 ($NCH_2\underline{C}H=CH_2$). **IR (cm^{-1}) ν_{max} :** 2240. **MS: m/z (%):** 148 (M^+, 14), 147 (M^+-1, 67), 133 (30), 121 (48), 107 (36), 80 (34), 55 (100).

2-Propyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile 407e

Yield after chromatography = 58 %

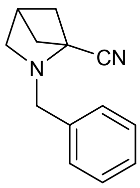
Yield after acid/base extraction = 67 %



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.97 (3H, t, *J*= 7.4 Hz, CH_3), 1.57 (2H, sext, *J*= 7.6 Hz, $NCH_2C\underline{H}_2CH_3$), 1.87 (2H, dd (+ 2 sym. side lines), *J*= 4.5 Hz, *J*= 1.8 Hz, (*J*= 11.5 Hz from centre of signal), CH_2 ring), 2.07 (2H, br. s, CH_2 ring), 2.62 (2H, t, *J*= 7.6 Hz, $NC\underline{H}_2CH_2CH_3$), 2.74 (3H, br. s, NCH_2 ring + CH ring). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 11.84 (CH_3), 22.07 ($NCH_2\underline{C}H_2CH_3$), 38.94 (CH ring), 42.05 (CH_2 ring), 55.18 (NCH_2 ring), 55.63 ($N\underline{C}H_2CH_2CH_3$), 59.50 ($C_{quat.}$), 117.93 (CN). **IR ($cm^{-1}$) ν_{max} :** 2241. **MS: m/z (%):** 150 (M^+, 9), 135 (11), 121 (100), 107 (13), 93 (17).

2-Benzyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile 407f

Yield after acid/base extraction = 73 %

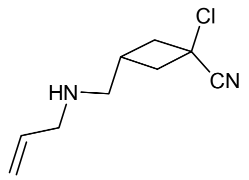


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.96 (2H, dd (+ 2 sym side lines), *J*= 1.8 Hz, *J*= 4.5 Hz, (*J*= 11.4 Hz from centre of signal), CH_2 ring), 2.12-2.15 (2H, m, CH_2 ring), 2.65 (2H, s, CH_2N), 2.71-2.74 (1H, m, CH ring), 3.87 (2H, s, NCH_2Ph). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 38.99 (CH ring), 42.05 (CH_2 ring), 54.82 (NCH_2 ring), 57.50 (NCH_2Ph), 59.42 ($C_{quat.}$ ring), 117.77 (CN), 127.19 (CH), 128.34 (CH), 128.55 (CH), 138.29 ($C_{quat.}$, Ph). **IR (cm^{-1}) ν_{max} :** 2240. **MS: m/z (%):** 198 (M^+, 17), 197 (20), 183 (4), 157 (5), 130 (5), 104 (8), 92 (17), 91 (100), 65 (19).

6.12.4.1. Ring opening of 2-allyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile

3-[(Allylamino)methyl]-1-chlorocyclobutane carbonitrile 412

This compound was formed in an attempt to remove the allyl group from nitrogen. 0.20 g Of 2-allyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile was dissolved in 3 ml of $ClCH_2CH_2Cl$ and cooled to 0°C in an ice bath. 0.29 g (1.5 equiv.) Of ACE was added and kept at 0°C for 15 minutes. The mixture was subsequently heated under reflux for 1 hour. All the solvent was evaporated and 4 ml of MeOH was added. The solution was again refluxed for 1 hour and evaporated once more. An oil of 0.17 g was obtained which was almost pure 3-[(allylamino)methyl]-1-chlorocyclobutane carbonitrile (yield = 69%).

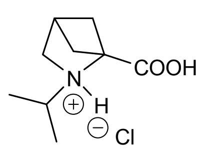


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.50 (1H, br. s, NH), 1.99-2.07 (2H, m, CH_2 ring), 2.65-2.73 (2H, m, CH_2 ring), 2.72-2.87 (1H, m, CH ring), 3.28 (2H, d, J= 5.6 Hz, NC$\underline{H}_2$CH), 3.63 (2H, d, J= 6.3 Hz, NC$\underline{H}_2$CH=CH_2), 5.13-5.30 (2H, m, CH=C$\underline{H}_2$), 5.82-5.98 (1H, m, C$\underline{H}$=CH_2). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 30.01 (CH ring), 36.89 (CH_2 ring), 46.96 (NCH_2), 47.93 (N$\underline{C}H_2$CH=CH_2), 49.83 ($C_{quat.}$ ring), 116.48 (CH=$\underline{C}H_2$), 121.46 (CN), 134.91 ($\underline{C}$H=CH_2). **IR (cm^{-1}) ν_{max} :** 2219 (CN). **MS: m/z (%):** (GC) 185/183 (M^++1, 6), 170/168 (6), 143 (5), 107 (20), 93 (23), 81 (100), 41 (72).

6.12.5. Synthesis of 2-alkyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochlorides

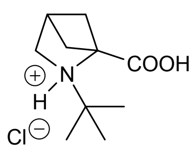
An amount of 0.2 g of 2-alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile was dissolved in 3 ml of a 6N hydrochloric acid solution. The reaction mixture was refluxed overnight and evaporated under reduced pressure. Distilled water was added and evaporated again. The amino acids were crystallised from water and methanol (1/1). To obtain mass spectra, the amino acids were derivatised to the corresponding methyl esters using diazomethane under standard conditions.

2-isopropyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride 408a



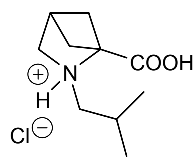
^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.30 (6H, d, J = 6.6 Hz, CH_3), 1.92-2.04 (2H, m, CH_2 ring), 2.34-2.40 (2H, m, CH_2 ring), 2.88 (1H, br. s, CH ring), 3.44 (1H, d, J = 9.9 Hz, NC$\underline{H}_a$$H_b$), 3.71 (1H, d, J = 9.9 Hz, NC$H_a$$\underline{H}_b$), 3.84 (1H, sept, J = 6.6 Hz, NC$\underline{H}$(CH_3)$_2$). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 18.41 (CH_3), 19.33 (CH_3), 35.61 (CH ring), 36.28 (CH_2 ring), 45.42 (CH_2 ring), 56.94 (NCH), 57.14 (NCH_2 ring), 75.99 ($C_{quat.}$), 169.84 (COOH). **IR (cm^{-1}) ν_{max} :** (KBr) 1728. **MS: m/z (%):** (methyl ester, from the reaction with diazomethane) (GC) 183 (M^+, 34), 168 (81), 124 (22), 108 (26), 82 (100). yield = 78 %.

2-t-butyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride 408b



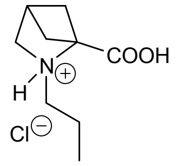
^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.40 (9H, s, t-Bu), 1.95-2.31 (4H, m, CH_2 ring), 2.79 (1H, br. s, CH ring), 3.59-3.64 (2H, m, NCH_2 ring). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 26.61 (t-Bu), 33.98 (CH ring), 37.43 (CH_2 ring), 45.17 (CH_2 ring), 55.32 (NCH_2 ring), 66.12 ($C_{quat.}$, t-Bu), 75.36 ($C_{quat.}$ ring), 170.29 (COOH). **IR (cm^{-1}) ν_{max} :** (KBr) 1723. **MS: m/z (%):** (methyl ester, from the reaction with diazomethane) (GC) 197 (M^+, 24), 182 (12), 126 (27), 109 (100), 82 (47), 81 (56), 57 (22). Yield = 68 %.

2-isobutyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride 408c



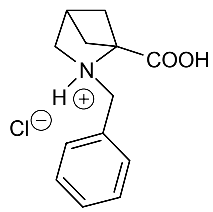
[1]H-NMR (270 MHz, D_2O, CH_3CN) δ: 0.98 (3H, d, *J*= 5.3 Hz, CH_3), 1.0 (3H, d, *J*= 6.6 Hz, CH_3), 1.97-2.15 (3H, m, CH_2 ring + $NCH_2C\underline{H}(CH_3)_2$), 2.43 (2H, br. d, *J*= 7.6 Hz, CH_2 ring), 2.92 (1H, br s, CH ring), 3.01 (1H, dd, *J*= 12.5 Hz, *J*= 5.9 Hz, $NC\underline{H}_aH_bCH(CH_3)_2$), 3.26 (1H, dd, *J*= 12.5 Hz, *J*= 8.3 Hz, $NCH_a\underline{H}_bCH(CH_3)_2$), 3.42 (1H, d, *J*= 9.6 Hz, $NC\underline{H}_aH_b$ ring), 3.85 (1H, d, *J*= 9.6 Hz, $NCH_a\underline{H}_b$ ring). **[13]C-NMR (68 MHz,D_2O, CH_3CN) δ:** 20.26 (CH_3), 20.63 (CH_3), 25.94 ($NCH_2\underline{C}H(CH_3)_2$), 36.97 ($CH_2$ ring + CH ring), 43.49 (CH_2 ring), 60.04 (NCH_2 ring), 60.83 ($N\underline{C}H_2CH(CH_3)_2$), 77.56 ($C_{quat.}$), 167.80 (COOH). **IR ($cm^{-1}$) ν_{max} :** (KBr) 1736. **MS: m/z (%):** (methyl ester, from the reaction with diazomethane) (GC) 197 (M^+, 7), 182 (9), 154 (100), 138 (19), 82 (24). Yield = 82 %.

2-Propyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride 408d



[1]H-NMR (270 MHz, D_2O, CH_3CN) δ: 0.94 (3H, t, *J*= 7.3 Hz, CH_3), 1.71-1.77 (2H, m, $NCH_2C\underline{H}_2CH_3$), 1.90-2.05 (2H, m, CH_2 ring), 2.42-2.45 (2H, m, CH_2 ring), 2.92 (1H, br. s, CH ring), 2.95-3.05 (1H, m, $NC\underline{H}_aH_bCH_2CH_3$), 3.35 (1H, d, *J*= 9.4 Hz, $NC\underline{H}_aH_b$ ring), 3.36-3.47 (1H, m, $NCH_a\underline{H}_bCH_2CH_3$), 3.78 (1H, d, *J*= 9.4 Hz, $NCH_a\underline{H}_b$ ring). **[13]C-NMR (68 MHz, D_2O, CH_3CN) δ:** 11.16 ($NCH_2CH_2\underline{C}H_3$), 18.98 ($NCH_2\underline{C}H_2CH_3$), 36.70 (CH ring + CH_2 ring), 43.51 (CH_2 ring), 54.18 ($N\underline{C}H_2CH_2CH_3$), 58.75 ($NCH_2$ ring), 76.48 ($C_{quat.}$), 167.60 (COOH). **IR (cm^{-1}) ν_{max} :** (KBr) 1730. **MS: m/z (%):** (methyl ester, from reaction with diazomethane) (GC) 183 (M^+, 18), 168 (43), 154 (99), 124 (74), 82 (100). Yield = 85 %.

2-Benzyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride 408e

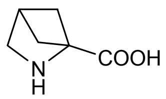


[1]H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.92 (1H, dd, *J*≈ 10.1 Hz, *J*≈ 10.1 Hz, $C\underline{H}_aH_b$ ring), 2.16 (1H, dd, *J*≈ 10.1 Hz, *J*≈ 10.1 Hz, $CH_a\underline{H}_b$ ring), 2.44-2.52 (2H, m, CH_2 ring), 2.91 (1H, br. t, *J*= 3.2 Hz, CH ring), 3.43 (1H, d, *J*= 11.6 Hz, CH_aH_bN ring), 3.47 (1H, d, *J*= 11.6 Hz, CH_aH_bN), 4.14 (1H, d, *J*= 12.7 Hz, $C\underline{H}_aH_bPh$), 4.73 (1H, d, *J*= 12.7 Hz, $CH_a\underline{H}_bPh$), 7.45-7.52 (5H, m, CH, Ph). **[13]C-NMR (68 MHz, D_2O, CH_3CN) δ:** 37.07 (CH ring), 37.16 (CH_2 ring), 44.06 (CH_2 ring), 56.74 (CH_2N), 58.83 (CH_2N), 77.68 ($C_{quat.}$ ring), 130.40 (CH), 130.67 (CH), 131.08 (CH), 131.58 ($C_{quat.}$ Ph), 168.71 (COOH). **IR (cm^{-1}) ν_{max} :** (KBr) 1732. **MS: m/z (%):** (methyl ester, from reaction with diazomethane) (GC) 231 (M^+, 10), 230 (9), 216 (12), 172 (19), 91 (100), 65 (11), 55 (19). Yield = 88 %.

6.12.5.1. Synthesis of 2,4-methanoproline

2,4-Methanoproline 3

A suspension of 0.05 g (0.197 mmol) of 2-benzyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride and 0.02g of Pd/C (0.1 equiv.; 10% Pd/C) in 1 ml of dry methanol was stirred at room temperature in a H_2-bottle (5 bar H_2). After stirring overnight, the suspension was filtered over celite and 0.03 g of 2,4-methanoproline hydrochloride was obtained (99%). Removal of the hydrochloride using Dowex 50 (H+ form) gave the natural 2,4-methanoproline. The assignment of H_c +H_d should be 1.71 ppm instead of 1.17 ppm; The authors have corrected this mistake in one of the following articles[38] and was confirmed by our own spectral data.

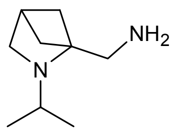


^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.71 (2H, dd (+ 2 sym side lines), *J*= 2.3 Hz, *J*= 6.2 Hz (9.5) CH_2 ring), 2.31-2.33 (2H, m, CH_2 ring), 2.90 (1H, br. t, *J*= 3.2 Hz, CH ring), 3.40 (2H, br. s, NCH_2 ring). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 38.0 (CH), 41.3 (CH_2 ring), 50.4 (CH_2N), 75.2 ($C_{quat.}$), 173.0 (C=O).

6.12.6. Synthesis of (2-alkyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine

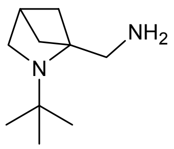
A solution of 0.2 g (1.4 mmol) 2-alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile in 10 ml of dry ether was slowly added to a solution of 1.5 equiv. of $LiAlH_4$ in 1 ml of dry ether at 0°C. The reaction was stirred overnight at room temperature, followed by careful addition of water to neutralize the excess of lithium aluminium hydride. The mixture was filtered over celite and washed with ether. The filtrate was dried overnight on magnesium sulphate, filtered and evaporated to give the pure (2-alkyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine as an oil (purity >97 %).

(2-isopropyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine 414a



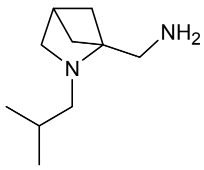
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.04 (6H, d, *J*= 6.3 Hz, CH_3), 1.46 (2H, dd (+ 2 sym. side lines), *J*= 4.3 Hz, *J*= 1.3 Hz, (*J*= 11.2 Hz from centre of signal), CH_2 ring), 1.53-1.55 (2H, m, CH_2 ring), 2.63 (1H, br. s, CH ring), 2.84 (2H, br. s, NCH_2), 2.92 (2H, br. s, CH_2NH_2), 3.24 (1H, sept, *J*= 6.4 Hz, NC$\underline{H}$(CH_3)$_2$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 20.16 (CH_3), 34.59 (CH ring), 39.32, (CH_2 ring), 42.41 (CH_2NH_2), 47.67 (NCH_2 ring), 48.82 (N$\underline{C}$H(CH_3)$_2$), 74.32 ($C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 3292, 1604. **MS: m/z (%):** (GC) 154 (M^+, 41), 139 (11), 124 (26), 82 (100). Yield = 78 %.

(2-t-butyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine 414b



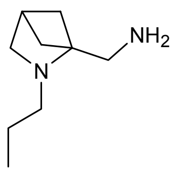
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.17 (9H, s, t-Bu), 1.50-1.54 (4H, m, 2 x CH_2 ring), 2.58 (1H, br. s, CH ring), 2.97 (2H, br. s, CH_2N), 3.04 (2H, br. s, NCH_2). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 28.66 (CH_3, t-Bu), 33.85 (CH ring), 39.32 (CH_2 ring), 44.98 (CH_2NH_2), 53.08 (NCH_2 ring), 54.72 ($C_{quat.}$, t-Bu), 76.19 ($C_{quat.}$, ring). **IR (cm^{-1}) ν_{max} :** 1583. **MS: m/z (%):** (GC) 168 (M^+, 52), 153 (10), 112 (17), 111 (30), 96 (20), 95 (100), 94 (49), 82 (57), 67 (34), 57 (34), 55 (70). Yield = 92 %.

(2-isobutyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine 414c



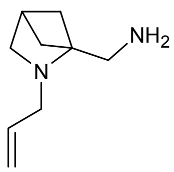
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.95 (6H, d, *J*= 6.6 Hz, CH_3), 1.43-1.48 (4H, m, CH_2 ring), 1.67 (1H, sept, *J*= 6.6 Hz, $NCH_2C\underline{H}(CH_3)_2$), 2.16 (2H, d, *J*= 6.9 Hz, $NC\underline{H}_2CH(CH_3)_2$), 2.63 (1H, br. s, CH ring), 2.70 (2H, br. s, CH_2N), 2.84 (2H, br. s, CH_2N). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 21.22 (CH_3, t-Bu), 27.87 ($NCH_2\underline{C}H(CH_3)_2$), 36.42 (CH ring), 37.72 (CH_2 ring), 42.26 (CH_2NH_2), 58.35 (CH_2N), 59.64 (CH_2N), 74.18 ($C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 3290, 1580. **MS: m/z (%):** (GC) 168 (M^+, 47), 138 (26), 125 (74), 96 (70), 82 (100), 57 (35). Yield = 84 %.

(2-propyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine 414d



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.94 (3H, t, *J*= 7.3 Hz, $NCH_2CH_2C\underline{H}_3$), 1.46-1.58 (6H, m, 2 x CH_2 ring + $NCH_2C\underline{H}_2CH_3$), 1.60-1.67 (2H, br. s, NH_2), 2.36 (2H, t, *J*= 7.9 Hz, $NC\underline{H}_2CH_2CH_3$), 2.65 (1H, br. s, CH ring), 2.75 (2H, br. s, NCH_2), 2.88 (2H, br. s, CH_2N). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 12.18 (CH_3), 22.19 ($NCH_2\underline{C}H_2CH_3$), 36.24 (CH ring), 37.41 (CH_2 ring), 42.28 ($\underline{C}H_2NH_2$), 53.31 (NCH_2), 57.57 (NCH_2), 74.48 ($C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 3292, 1583. **MS: m/z (%):** (GC) 154 (M^+, 56), 125 (41),124 (51), 96 (48), 82 (100). Yield = 91 %.

(2-allyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine 414e

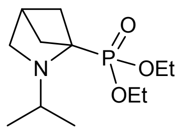


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.46-1.58 (6H, m, 2 x CH_2 ring + NH_2), 2.64 (1H, br. s, CH ring), 2.73 (2H, br. s, NCH_2 ring), 2.88 (2H, br. s, $C\underline{H}_2NH_2$), 3.09 (2H, d, *J*= 6.3 Hz, $NC\underline{H}_2CH{=}CH_2$), 5.08-5.12 (1H, m, $NCH_2CH{=}C\underline{H}_aH_b$), 5.21 (1H, dq, *J*= 17.2 Hz, *J*= 1.7 Hz, $NCH_2CH{=}CH_a\underline{H}_b$), 5.94 (1H, ddt, *J*= 17.2 Hz, *J*= 10.2 Hz, *J*= 6.3 Hz, $NCH_2C\underline{H}{=}CH_2$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 36.26 (CH ring), 37.41 (CH_2 ring), 42.19 (CH_2NH_2), 54.59 ($N\underline{C}H_2CH{=}CH_2$), 57.23 ($NCH_2$ ring), 74.61 ($C_{quat.}$), 116.48 ($NCH_2CH{=}\underline{C}H_2$), 136.55 ($NCH_2\underline{C}H{=}CH_2$). **IR ($cm^{-1}$) ν_{max} :** 3366, 1448. **MS: m/z (%):** (GC) 152 (M^+, 43), 122 (100), 108 (54), 94 (60), 82 (62). Yield = 82 %.

6.12.7. Synthesis of diethyl 2-isopropyl-2-azabicyclo[2.1.1]hex-1-ylphosphonate

Diethyl 2-isopropyl-2-azabicyclo[2.1.1]hex-1-ylphosphonate 416

To a solution of 0.52 g diethylphosphite (2 equiv.) in 4 ml of dichloroethane, 0.4 g triethyl amine (2.1 equiv.) was added. The mixture was cooled to 0°C, 0.46 g chlorotrimethylsilane (2.2 equiv.) was added and stirring was continued for 1h at room temperature. At this temperature, 0.3 g N-[3-(chloromethyl)-1-cyclobutylidene]isopropylamine in 3 ml of dichloroethane was added and the reaction mixture was heated at 70°C for 5 days. After this period, water (+ 20 ml of Na_2CO_3) was added and extracted with dichloromethane. The organic phase was dried with $MgSO_4$. Filtration and evaporation of the solvent gave 0.56 g of a crude product which still contained some diethyl phosphite. This product was dissolved in diethyl ether and extracted with a 2N hydrogen chloride solution. The diethyl layer contained mostly diethyl phosphite. The water layer was basified with a 1N NaOH solution and extracted with dichloromethane. The organic layer was dried again with $MgSO_4$ overnight. Filtering off the drying agent and evaporating the solvent gave 0.15 g pure diethyl 2-isopropyl-2-azabicyclo[2.1.1]hex-1-ylphosphonate as an oil (yield = 31%).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.11 (6H, d, *J*= 6.6 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.35 (6H, t, *J*= 7.1 Hz, 2 x OCH_2C<u>H</u>$_3$), 1.76 (2H, d, *J*= 3.6 Hz, CH_2 ring), 2.04 (2H, br. s, CH_2 ring), 2.77 (1H, dd, *J*= 19.1 Hz, *J*= 3.0 Hz, CH ring), 2.93 (2H, br. s, NCH_2), 3.73 (1H, sept, *J*= 6.6 Hz, NC<u>H</u>(CH_3)$_2$), 4.11-4.22 (4H, m, OC<u>H</u>$_2$$CH_3$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** O (TMS), 16.53 (d, *J*= 4.9 Hz, OCH_2<u>C</u>H$_3$), 16.66 (NCH(<u>C</u>H$_3$)$_2$), 37.56 (d, *J*= 26.9 Hz, CH ring), 41.71 (2 x CH_2 ring), 47.30 (d, *J*= 13.4 Hz, NCH_2), 50.30 (N<u>C</u>H(CH_3)$_2$), 62.04 (d, *J*= 6.1 Hz, O<u>C</u>H$_2$$CH_3$), 67.81 (d, *J*= 174.6 Hz, $C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 1255. **MS: m/z (%):** (GC) 261 (M^+, 20), 246 (M^+-CH_3, 15), 220 (16), 218 (18), 190 (12), 124 (31), 82 (100). **^{31}P-NMR (109 MHz, $CDCl_3$) δ:** 21.55 ppm.

6.12.8. Synthesis of 2,4-methanoproline

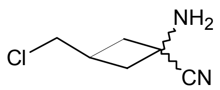
1-Amino-3-(chloromethyl)cyclobutane carbonitrile 420

There are several ways to synthesise this compound but the main problem lies in its purification. This compound is unstable under all basic conditions, so even a fast acid/base extraction leads to some extent to degradation.

In the first method, 0.5 g of 3-(chloromethyl)cyclobutanone was dissolved in 5 ml of dry MeOH and 0.55 g of ammonium formate (2 equiv.) was added while stirred for 3 h at room temperature under a N_2-atmosphere. The reaction mixture was cooled to 0°C when 0.85 g of trimethylsilyl cyanide was added. After slowly allowing the solution to warm to room temperature overnight, the solvent was removed under reduced pressure and a white powder in an oil was obtained. The excess of ammonium formate and salts were removed by dissolving the mixture in dichloromethane and passing it through a very short silica column (2 or 3 cm). The pure product (mixture of diastereoisomers) was stripped off using dichloromethane. 0.49 g (yield 81 %) of 1-amino-3-(chloromethyl)cyclobutane carbonitrile was obtained as an oil.

This compound can also be prepared by using ammonium acetate or HMDS (hexamethyldisilazane) or ammonia (NH_3, 7N solution in MeOH). The same amounts and conditions as described above can be used.

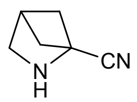
In another method 0.2 g of 3-(chloromethyl)cyclobutanone was dissolved in 2 ml of MeOH and 0.73 g of acetone cyanohydrine (5 equiv.) was added. 0.45 g of ammonium chloride was dissolved in 2 ml of distilled water and added to the prepared solution in MeOH. This mixture was heated under reflux for 1 day, then it was cooled and extracted with dichloromethane (do not use base or $NaHCO_3$). The organic phase was dried with $MgSO_4$ overnight. Filtering off the $MgSO_4$ and evaporating the solvent gave 0.15 g of pure 1-amino-3-(chloromethyl)cyclobutane carbonitrile as a clear oil (yield = 62 %; 81/19).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR, *MINOR*, not assigned: 2.18-2.27 (2H, m, CH_2 ring), *2.44-2.60* (4H, m, CH_2 ring), 2.54-2.72 (1H, m, CH ring), 2.78-2.86 (2H, m, CH_2 ring), *2.89-3.03* (1H, m, CH ring), 3.61 (2H, d, *J*= 6.6 Hz, CH_2Cl), *3.64* (2H, d, *J*= 7.3 Hz, CH_2Cl). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 27.85 (CH ring), *30.89* (CH ring), *39.07* (CH_2 ring), 39.89 (CH_2 ring), 47.91 (CH_2Cl), *48.00* (CH_2Cl), 62.60 ($C_{quat.}$), *121.15* (CN), 121.83 (CN). **IR (cm^{-1}) ν_{max} :** 3412 (br.), 2240 (CN). **MS: m/z (%):** (GC) MAJOR: no M^+, 120/118 (M^+-CN, 11), 110 (8), 90 (12), 83 (39), 76 (10), 70 (10), 69 (10), 55 (67), 43 (14), 42 (100); MINOR: no M^+, 120/118 (10), 110 (8), 90 (14), 83 (39), 76 (10), 70 (12), 55 (67), 42 (100).

2-Azabicyclo[2.1.1]hexane-1-carbonitrile 419

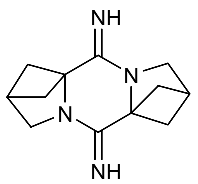
Up to now, no ideal reaction conditions exist to make this compound in a pure form. In the best procedure 0.2 g of 3-(chloromethyl)cyclobutanone was dissolved in 5 ml of MeOH (dry) and 1.2 ml of NH_3 solution was added (7N NH_3 in MeOH) together with 0.29 g (2 equiv.) of acetone cyanohydrine. This mixture was heated in a closed vessel (headspace 5 times the volume of the liquid) at 100°C overnight. After 12h the solvent was evaporated and the resulting oil was distilled and gave 0.06 g of 2-azabicyclo[2.1.1]hexane-1-carbonitrile (yield = 32 %).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.66 (2H, dd (+ 2 sym side lines), *J*= 4.5 Hz, *J*= 1.8 Hz, (*J*= 11.6 Hz from centre of signal), CH_2 ring), 2.15-2.19 (2H, m, CH_2 ring), 2.85 (1H, br. td, *J*= 2.3 Hz, *J*= 1 Hz, CH ring), 3.30 (2H, br. s, CH_2N). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 39.07 (CH ring), 44.55 (CH_2 ring), 47.46 (CH_2N), 53.85 ($C_{quat.}$), 118.33 (CN). **IR (cm^{-1}) ν_{max} :** 2242 (CN). **MS: m/z (%):** (GC) 108 (M^+, 33), 107 (M^+-1, 77), 93 (100), 81 (41), 80 (44), 68 (17), 66 (16), 53 (35), 41 (48). **Bp**.= 100°C/0.5 mmHg.

Di(2’-azabicyclo[2.1.1]hexano)[1’, 2’-f:1’,2’-c]-2,5-diiminopiperazine 423

0.05 g 3-(chloromethyl)cyclobutanone was dissolved in 1 ml of MeOH, 0.12 ml of NH_3 solution was added (2 equiv.; 7N solution in MeOH) and 0.18 g acetone cyanohydrine (5 equiv.). 0.11 g Of ammonium chloride was dissolved in 1 ml of distilled water and added to the mixture described above. The mixture was heated at 100°C in a closed vessel overnight (headspace 5 times the volume liquid). The solvent was removed and the crude product was purified by column chromatography. A pure sample of 0.03 g of di(2’-azabicyclo[2.1.1]hexano)[1’, 2’-f:1’,2’-c]-2,5-diiminopiperazine (yield = 65%) was obtained as a viscous oil.

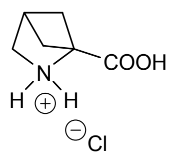


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.72 (4H, dd (+ 2 sym side lines), *J*= 4.6 Hz, *J*= 1.7 Hz, (*J*= 11.7 Hz from centre of signal), CH_2 ring), 2.05 (2H, s, NH), 2.51 (4H, br. s, CH_2 ring), 2.92-2.95 (2H, m, CH ring), 3.60 (4H, s, CH_2N). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 35.36 (2 x CH), 44.04 (4 x CH_2), 49.56 (2 x NCH_2), 72.63 (2 x $C_{quat.}$), 161.69 (2 x <u>C</u>=NH). **IR (cm^{-1}) ν_{max} :** 1653 (C=NH). **MS: m/z (%):** a) (ES, Pos) 219 (M^++1, 100). b) (GC) 219 (M^++1, 14), 218 (M^+, 100), 217 (20), 203 (30), 189 (21), 177 (39), 149 (19), 109 (21), 81 (39), 54 (21), 41 (32).

2,4-Methanoproline 422

The 2-azabicyclo[2.1.1]hexane-1-carbonitrile was dissolved in a 6N HCl solution (5% solution; 0.56 mmol) and heated under reflux during an overnight period. All the solvent was removed and 2,4-methanoproline was obtained as its hydrochloride salt (white powder, NaCl still present). No side products were formed and the HCl could be removed using Dowex (H^+ form).

2,4-Methanoproline could also be prepared by refluxing di(2’-azabicyclo[2.1.1]hexano)[1’, 2’-f:1’,2’-c]-2,5-diiminopiperazine (5% solution) in a mixture of 12N HCl/HOAc 1/1 during an overnight period. Workup is analogous as described above. For spectral data of the 2,4-methanoproline see page 157. The spectral data of the hydrochloride salt are reported below.



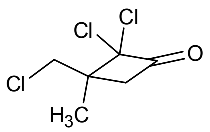
^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.79 (2H, dd (+ 2 sym side lines), *J*= 5.9 Hz, *J*= 2.3 Hz, (*J*= 12.4 Hz from centre of signal; 8.3 Hz from outside peaks), CH_2 ring), 2.39-2.40 (2H, m, CH_2 ring), 2.93 (1H, br. t, *J*= 2.8 Hz, CH ring), 3.43 (2H, br. s, CH_2N). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 38.00 (CH), 41.56 (CH_2 ring), 50.56 (NCH_2), 72.07 ($C_{quat.}$), 169.55 (COOH). **IR (cm^{-1}) ν_{max} :** 1725.

6.13. Entry to 2-azabicyclo[2.1.1]hexanes from methallyl chloride

6.13.1. Synthesis of 3-(chloromethyl)-3-methylcyclobutanone

2,2-Dichloro-3-(chloromethyl)-3-methylcyclobutanone 426

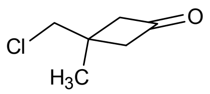
A solution of 35.34 g 3-chloro-2-methyl-1-propene (90 % pure, technical) in 180 ml of dry diethyl ether was stirred with 14.36 g of activated Zn/Cu complex under a N_2-atmosphere. To this solution a mixture of 5 ml of $POCl_3$, 20 ml of trichloroacetyl chloride in 140 ml of dry diethyl ether was slowly added over a period of 2 hours. The reaction was refluxed overnight. The workup was the same as for the synthesis of 3-(chloromethyl)-2,2-dichlorocyclobutanone. 7.69 g of pure 2,2-dichloro-3-(chloromethyl)-3-methylcyclobutanone was obtained as a liquid (yield = 21 %).



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.58 (3H, s, CH_3), 3.01 (1H, d, *J*= 17.5 Hz, C<u>H</u>$_a$H$_b$ ring), 3.37 (1H, d, *J*= 17.5 Hz, CH$_a$<u>H</u>$_b$ ring), 3.81 (1H, d, *J*= 11.3 Hz, C<u>H</u>$_a$H$_b$Cl), 3.91 (1H, d, *J*= 11.3 Hz, CH$_a$<u>H</u>$_b$Cl). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 21.46 (CH_3), 46.13 ($C_{quat.}$), 49.52 (CH_2Cl), 52.90 (<u>C</u>H$_2$C=O), 90.58 ($C_{quat.}$, <u>C</u>Cl$_2$), 191.21 (C=O). **IR (cm^{-1}) ν_{max} :** 1814. **MS: m/z (%):** (GC) no M^+, 160/158 (M^+-Cl, 100), 125 (65), 123 (83), 87 (25).

3-(Chloromethyl)-3-methylcyclobutanone 427

The same procedure and workup was applied as for the synthesis of the 3-(chloromethyl)cyclobutanone. Isolated yield 83 % (liquid).

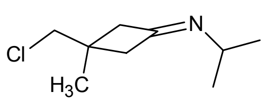


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.47 (3H, s, CH_3), 2.77-2.86 (2H, m, CH_2 ring), 3.03-3.11 (2H, m, CH_2 ring), 3.71 (2H, s, CH_2Cl). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 24.12 (CH_3), 31.05 ($C_{quat.}$), 53.58 (CH_2Cl), 56.15 (CH_2 ring), 205.01 (C=O). **IR (cm^{-1}) ν_{max} :** 1784. **MS: m/z (%):** (GC) 134/132 (M^+, 8), 92 (23), 90 (71), 69 (88), 68 (32), 55 (100).

6.13.2. Synthesis of N-[3-(chloromethyl)-3-methylcyclobutylidene]isopropyl-amine

N-[3-(Chloromethyl)-3-methylcyclobutylidene]isopropylamine 428

The same procedure was followed as for the preparation of the synthesis of N-[3-(chloromethyl)-1-cyclobutylidene]amines. Isolated yield = 83 % (oil).



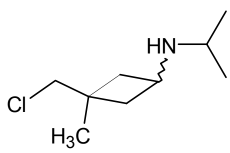
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.11 (3H, d, *J*= 6.3 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.12 (3H, d, *J*= 6.3 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.36 (3H, s, CH_3), 2.56-2.69 (2H, CH_2 ring), 2.78-2.87 (2H, m, CH_2 ring), 3.41 (1H, sept, *J*= 6.3 Hz, NC<u>H</u>), 3.61

(2H, s, CH_2Cl). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 23.61 (NCH(<u>C</u>H$_3$)$_2$), 24.31 (CH_3), 33.78 ($C_{quat.}$), 43.76 (CH_2 ring), 47.22 (CH_2 ring), 52.08 (NC<u>H</u>), 53.94 (CH_2Cl), 162.91 (<u>C</u>=N). **IR (cm^{-1}) ν_{max} :** 1668. **MS: m/z (%):** (GC) 174/176 (M^++1, 9), 139 (M^+-Cl, 14), 123 (21), 83 (100), 55 (58).

6.13.3. Reduction of N-[3-(chloromethyl)-3-methylcyclobutylidene]isopropylamine

3-(Chloromethyl)-N-isopropyl-3-methylcyclobutanamine 437

0.25 g of N-[3-(chloromethyl)-3-methylcyclobutylidene]isopropylamine was dissolved in 5 ml of dry THF and added to a dry flask (under a N_2-atmosphere at 0°C) containing 0.09 g (1.5 equiv.) $LiAlH_4$. When all the starting material was added, the reaction was heated under reflux for 1 day. After cooling the mixture, some drops of water were added until bubbling ceased. The suspension was filtered over a mixture of $MgSO_4$ and celite (1/1) and the filtrate was evaporated. After purification by column chromatography, 0.06 g of 3-(chloromethyl)-N-isopropyl-3-methylcyclobutanamine was retrieved as a viscous oil (yield = 24 %). Severe losses of product occurred during column chromatography and only one of the two possible stereoisomers could be isolated.



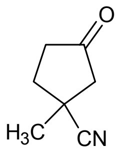
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.02 (6H, d, J= 6.3 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.20 (3H, s, CH_3), 1.54 (2H, ddd, J= 10.2 Hz, J= 7.9 Hz, J= 2.6 Hz, CH_2 ring), 2.32 (2H, ddd, J= 10.2 Hz, J= 7.6 Hz, J= 2.6 Hz, CH_2 ring), 2.80 (1H, sept, J= 6.3 Hz, NC<u>H</u>(CH$_3$)$_2$), 3.27 (1H, br. quint, J= 7.9 Hz, NCH ring), 3.54 (2H, br. s, CH_2Cl). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 23.36 (NCH(<u>C</u>H$_3$)$_2$), 26.83 (CH_3), 34.50 ($C_{quat.}$ ring), 40.99 (CH_2 ring), 45.77 (NCH), 46.85 (NCH), 54.86 (CH_2Cl). **IR (cm^{-1}) ν_{max} :** 2965. **MS: m/z (%):** a) (ES, Pos) 176/178 (M^++H, 100); b) (GC) no M^+, 160 (1), 126 (2), 85 (72), 70 (100), 43 (10). **Chromatography**: 100% EtOAc strip of impurities than 96/4 EtOAc/MeOH strip of compound.

6.13.4. Ring expansion of 3-(chloromethyl)-3-methylcyclobutanone

1-Methyl-3-oxocyclopentane carbonitrile 430

This compound was isolated in an attempt to close the N-[3-(chloromethyl)-3-methylcyclobutylidene]isopropylamine using acetone cyanohydrine. 0.8 g of N-[3-(chloromethyl)-3-methylcyclobutylidene]isopropylamine were dissolved in 15 ml of dry MeOH and 1.18 g (3 equiv.) of acetone cyanohydrine was added. The resulting solution was refluxed for 5 days when all the solvent was removed under reduced pressure. When performing an acid base extraction, it was observed that after evaporating the organic layers, much product was retrieved in the HCl diethyl ether extract and almost nothing in the dichloromethane $NaHCO_3$ extract.

When the HCl extract was purified by means of chromatography 0.28 g of 1-methyl-3-oxocyclopentane carbonitrile was obtained as an oil (yield = 49 %).

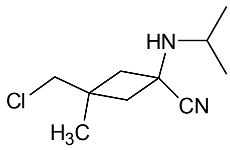


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.56 (3H, s, CH_3), 2.03-2.15 (1H, m, C<u>H</u>$_a$H$_b$), 2.29 (1H, d, *J*= 18.2 Hz, C<u>H</u>$_a$H$_b$C=O), 2.33-2.57 (3H, m, CH$_a$<u>H</u>$_b$, C<u>H</u>$_2$), 2.75 (1H, d, *J*= 18.2 Hz, CH$_a$<u>H</u>$_b$C=O). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** (C$_{quat.}$ overlaps), 24.49 (CH_3), 34.84 (CH_2), 36.39 (CH_2), 49.72 (CH_2), 123.72 (CN), 213.38 (C=O). **IR (cm^{-1}) ν$_{max}$:** 1748 (C=O), 2237 (CN). **MS: m/z (%):** (GC) 123 (M^+, 46), 95 (23), 94 (35), 67 (100), 55 (62). **Chromatography**: 65/35 Hex/EtOAc R$_f$= 0.23.

6.13.5. Synthesis of 3-(chloromethyl)-1-(isopropylamino)-3-methylcyclobutane carbonitrile

3-(Chloromethyl)-1-(isopropylamino)-3-methylcyclobutane carbonitrile 431

This compound was prepared using the same procedure as the first method to prepare 1-amino-3-(chloromethyl)cyclobutane carbonitrile except that, instead of ammonium formate, 1 equiv. of isopropyl amine was used and that the solvent only had to be removed. No purification was necessary (yield = 98%; liquid; 59/41).

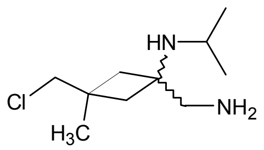


^{1}H-NMR (270 MHz, CDCl$_3$) δ: MAJOR: 1.09 (6H, d, *J*= 6.3 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.41 (3H, s, CH_3), 2.19 (2H, d, *J*= 13.2 Hz, C<u>H</u>$_a$H$_b$ ring), 2.42 (2H, d, *J*= 13.2 Hz, CH$_a$<u>H</u>$_b$ ring), 3.07-3.16 (1H, m, NC<u>H</u>(CH$_3$)$_2$), 3.60 (2H, s, CH_2Cl); MINOR: 1.15 (6H, d, *J*= 6.6 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.33 (3H, s, CH_3), 2.04 (2H, d, *J*= 13.3 Hz, C<u>H</u>$_a$H$_b$ ring), 2.62 (2H, d, *J*= 13.3 Hz, CH$_a$<u>H</u>$_b$ ring), 3.07-3.16 (1H, m, NC<u>H</u>(CH$_3$)$_2$), 3.66 (2H, s, CH_2Cl). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** MAJOR: 23.52 (NCH(<u>C</u>H$_3$)$_2$), 25.25 (CH_3), 34.56 (C$_{quat.}$), 44.15 (CH_2 ring), 45.35 (C$_{quat.}$), 46.92 (N<u>C</u>H(CH$_3$)$_2$), 54.73 (CH_2Cl), 122.53 (CN); MINOR: 23.47 (NCH(<u>C</u>H$_3$)$_2$), 26.13 (CH_3), 34.75 (C$_{quat.}$), 44.04 (CH_2 ring), 45.09 (C$_{quat.}$), 47.01 (NCH), 54.14 (CH_2Cl), 122.39 (CN). **IR (cm^{-1}) ν$_{max}$:** 2220. **MS: m/z (%):** (GC) major: 187/185 (M^+-CH_3, 7), 122 (15), 95 (23), 83 (100), 55 (38), 41 (82); minor: 187/185 (M^+-CH_3, 8), 122 (15), 95 (22), 83 (100), 55 (37), 43 (39), 41 (79).

6.13.5.1. Reduction of 3-(chloromethyl)-1-(isopropylamino)-3-methylcyclobutane carbonitrile

1-(Aminomethyl)-3-(chloromethyl)-N-isopropyl-3-methylcyclobutanamine 436a,b

The same conditions and equivalents of reagent were used as in the preparation of 3-(chloromethyl)-N-isopropyl-3-methylcyclobutanamine. The yield after chromatography was 45 % (54/46; oil). Severe losses of product occurred during column chromatography.



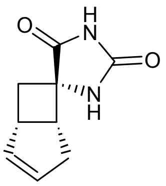
^{1}H-NMR (270 MHz, CDCl$_3$) δ: MAJOR: 1.06 (6H, d, *J*= 6.3 Hz, NCH(C$\underline{H}_3$)$_2$), 1.22 (3H, s, CH$_3$), 1.74 (2H, d, *J*= 12.5 Hz, C$\underline{H}_a$H$_b$ ring), 1.83 (2H, d, *J*= 12.5 Hz, CH$_a\underline{H}_b$ ring), 2.74 (2H, s, C$\underline{H}_2$NH$_2$), 2.67-2.84 (1H, m, NC$\underline{H}$(CH$_3$)$_2$), 3.56 (2H, s, CH$_2$Cl); MINOR: 1.05 (6H, d, *J*= 6.3 Hz, NCH(C$\underline{H}_3$)$_2$), 1.31 (3H, s, CH$_3$), 1.63 (2H, d, *J*= 13.5 Hz, C$\underline{H}_a$H$_b$ ring), 1.92 (2H, d, *J*= 13.5 Hz, CH$_a\underline{H}_b$ ring), 2.66 (2H, s, C$\underline{H}_2$NH$_2$), 2.67-2.84 (1H, m, NC$\underline{H}$(CH$_3$)$_2$), 3.48 (2H, s, CH$_2$Cl). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** MAJOR: 25.41 (NCH($\underline{C}$H$_3$)$_2$), 27.46 (CH$_3$), 32.26 (C$_{quat.}$), 41.78 (CH$_2$ ring), 43.61 ($\underline{C}$H$_2$NH$_2$), 48.95 (N$\underline{C}$H(CH$_3$)$_2$), 53.24 (C$_{quat.}$), 55.88 (CH$_2$Cl); MINOR: 25.53 (NCH($\underline{C}$H$_3$)$_2$), 27.15 (CH$_3$), 32.38 (C$_{quat.}$), 41.83 (CH$_2$ ring), 43.54 (CH$_2$NH$_2$), 49.06 (N$\underline{C}$H(CH$_3$)$_2$), 53.31 (C$_{quat.}$), 56.50 (CH$_2$Cl). **IR (cm^{-1}) ν_{max} :** 3288 (br.), 2869. **MS: m/z (%):** (GC) 206/204 (M$^+$, 14), 176/174 (100), 132 (35), 97 (46), 96 (44), 84 (37), 55 (24); MINOR: 206/204 (M$^+$, 12), 176/174 (100), 132 (42), 97 (73), 83 (60), 55 (34). **Chromatography**: 100% EtOAc to strip of impurities, than 96/4 EtOAc/MeOH to strip of the compound.

6.14. Entry to 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton

6.14.1. Using the Bucherer-Bergs synthesis

cis-cyclopentyl[1,2-f]-1,3-diazaspiro[3,4]octan-2,4-dione 442

To a solution of 40 ml of distilled water and 50 ml of methanol, 6 g of bicyclo[3.2.0]hept-2-en-6-one, 2.97 g of ammonium chloride (1 equiv.), 11.74 g ammonium carbonate (2.2 equiv.) and 4.34 g potassium cyanide (1.2 equiv.) was dissolved and heated for 24 h at 60°C. During this period a white crystalline product precipitates from the reaction mixture. After 24 h the mixture is filtered and washed with 30 ml of distilled water. After drying, the white crystals were dried at high vacuum yielding 4.97 g (yield 50 %) of cis-cyclopentyl[1,2-f]-1,3-diazaspiro[3,4]octan-2,4-dione as a single diastereoisomer. The filtrate was evaporated and extracted with dichloromethane (2 x 50 ml) and water (50 ml). The organic phase was dried with MgSO$_4$, filtered and evaporated to give a mixture of the two diastereoisomers. This mixture was crystallised in a methanol:water (1:1) mixture and gave an extra 1.1 g of the desired diastereoisomer (11 %). The total yield of the *cis*-isomer is 61 %. The supernatant contains still ~1.1g (11%) of the mixture of isomers.

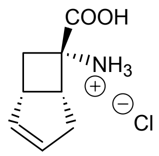


^{1}H-NMR (270 MHz, DMSO) δ: 1.81 (1H, dd, *J*= 12.2 Hz, *J*= 4.3 Hz, C$\underline{H}_a$H$_b$), 2.38-2.57 (2H, m, CH$_2$), 2.73 (1H, dd, *J*= 8.1 Hz, *J*= 12.4 Hz, CH$_a\underline{H}_b$), 3.02 (1H, br. s, CH), 3.18 (1H, br. t, *J*= 7.6 Hz, CH), 5.75-5.82 (2H, m, C$\underline{H}$=C$\underline{H}$). **^{13}C-NMR (68 MHz, DMSO) δ:** 33.32 (CH$_2$), 38.24 (CH$_2$), 39.19 (CH), 43.85 (CH), 61.72 (C$_{quat.}$), 131.97 (CH=), 133.31 (CH=), 156.89 (C=O), 178.81 (C=O). **IR (cm^{-1}) ν_{max} :** 1721 (br.). **MS: m/z (%):** (direct inlet) 178 (M$^+$, 7), 137 (6), 113 (9), 66 (100). **Mp.**: 245.9-246.3°C.

(1*S,5*R**,6*S**)-Ethyl 6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate 444**

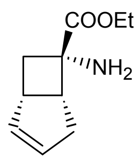
4.79 g of cis-cyclopentyl[1,2-f]-1,3-diazaspiro[3,4]octan-2,4-dione was dissolved in 160 ml of a 0.5N NaOH solution and refluxed for 24 h. The solvent was evaporated, 50 ml of distilled water was added and the solution was again evaporated. The hydrochloride salt was prepared by adding 50 ml of a 2N HCl solution followed by evaporation. Distilled water (50 ml) was added and evaporated. The resulting white powder was dried at high vacuum (0.05 mm Hg). A solution of 6.08 g of freshly distilled thionyl chloride was added at -15°C to a stirred solution of 50 ml of absolute ethanol. After 5 minutes the amino acid hydrochloride was added in one portion and kept at -15°C for 10 minutes. The reaction mixture was allowed to warm to 0°C and kept at this temperature during 30 minutes. After this period, the solution was refluxed for an additional 2h. Evaporation of the ethanol results in an oil which was dissolved in dichloromethane and extracted with a saturated $NaHCO_3$ solution until basic. The organic layer was washed with water and dried with $MgSO_4$. Filtration and evaporation gave 2.47g ethyl (1*S**,5*R**,6*S**)-6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate (yield 53 %; liquid).

(1*S,5*R**,6*S**)-6-Aminobicyclo[3.2.0]hept-2-ene-6-carboxylic acid hydrochloride**



^{1}H-NMR (270 MHz, D_2O, CH_3CN) δ: 1.91-2.07 (1H, m, $C\underline{H}_cH_d$), 2.42 (1H, br. d, *J*= 18.7 Hz, $C\underline{H}_aH_b$), 2.65 (1H, dd, *J*= 18.6 Hz, *J*= 9.4 Hz, $CH_a\underline{H}_b$), 2.95 (1H, dd, *J*= 13.7 Hz, *J*= 8.4 Hz, $CH_c\underline{H}_d$), 3.35 (1H, br. s, CH), 3.52 (1H, br. t, *J*= 8.1 Hz, CH), 5.86 (2H, m, CH=CH). **^{13}C-NMR (68 MHz, D_2O, CH_3CN) δ:** 34.28 (CH_2, 4), 36.94 (CH_2, 7), 41.54 (CH, 1), 42.44 (CH, 5), 59.33 ($C_{quat.}$), 132.82 (CH=), 135.48 (CH=), 175.30 (COOH). **IR (cm^{-1}) ν_{max} :** 3014 (br.), 1733. **MS: m/z (%):** (ES, Pos) 176 (M^++Na, 100), 154 (M^++H, 85). **Mp.**= 230°C (degradation).

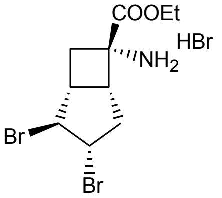
(1*S**,5*R**,6*S**)-Ethyl 6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate 444



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.31 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 1.59 (1H, dd, *J*= 12.5 Hz, *J*= 2.6 Hz, $C\underline{H}_{7a}H_{7b}$), 1.80 (2H, br. s, NH_2), 2.41-2.46 (1H, m, $CH_{4a}\underline{H}_{4b}$), 2.49-2.64 (1H, m, $C\underline{H}_{4a}H_{4b}$), 3.02 (1H, ddd, *J*= 12.4 Hz, *J*= 8.3 Hz, *J*= 1.0 Hz, $CH_{7a}\underline{H}_{7b}$), 3.14-3.21 (1H, m, CH 1), 3.19-3.27 (1H, m, CH 5), 4.21 (2H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 5.85 (2H, br. s, CH=CH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.23 (CH_3), 32.88 (CH_2, 4), 39.98 (CH_2, 7), 40.20 (CH, 1), 44.02 (CH, 5), 58.58 ($C_{quat.}$), 61.01 ($COO\underline{C}H_2CH_3$), 131.91 (CH=CH), 135.29 (CH=CH), 175.86 (COOEt). **IR (cm^{-1}) ν_{max} :** 1725 (COOEt). **MS: m/z (%):** (GC) no M^+, 152 (M^+-Et, 20), 135 (21), 115 (100), 108 (43), 71 (48).

ethyl (1*R**,2*S**,3*S**,5*R**,6*S**)-6-amino-2,3-dibromobicyclo[3.2.0]heptane-6-carboxylate hydrobromide 445

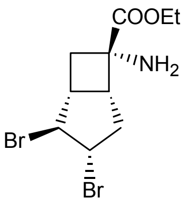
0.5 g of ethyl-6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate was dissolved in 5 ml of dry dichloromethane and was cooled to 0°C. 0.48 g Concentrated hydrogen bromide (1.02 equiv., 48% in water) was added and the solution was stirred at this temperature for 15 minutes. Bromine (0.45g, 1.02 equiv.) was dissolved in 5 ml of dichloromethane and added dropwise to the starting material at 0°C. The reaction was allowed to warm to room temperature overnight while a white precipitate was formed. Dry ether was added and the mixture was filtered and washed with some additional ether. The filtrate was concentrated up to 20% of the original volume and the white powder was filtered and washed with ether. The powder was dried at high vacuum and 1.01g (yield 87%) of 2,3-dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]-heptan-6-yl ammonium bromide was obtained. This product is not hygroscopic and is very stable when kept in a closed vessel.



^{1}H-NMR (270 MHz, DMSO) δ: 1.28 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.34-2.67 (2H, m, CH_2), 2.84-2.96 (3H, m, CH_2 + CH), 3.13-3.21 (1H, m, CH), 4.27 (2H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 4.30-4.42 (2H, m, 2 x CHBr). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 13.80 (CH_3), 34.59 (CH_2), 35.76 (CH_2), 40.81 (CH), 43.32 (CH), 54.05 ($C_{quat.}$), 54.75 (CHBr), 59.73 (CHBr), 62.30 ($COO\underline{C}H_2CH_3$), 170.32 ($\underline{C}OOEt$). **IR (cm^{-1}) ν_{max} :** (KBr) 1738. **MS: m/z (%):** (ES, Pos) 344/342/340 (M^++H-HBr, 100), 262/260 (15). **Mp.**= 187°C (degradation).

ethyl (1*R**,2*S**,3*S**,5*R**,6*S**)-6-amino-2,3-dibromobicyclo[3.2.0]heptane-6-carboxylate 446

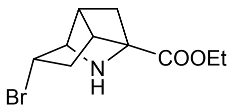
1.5 g (1*R**,2*S**,3*S**,5*R**,6*S**)-2,3-dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]-heptan-6-yl ammonium bromide was dissolved in 20 ml of dichloromethane and was extracted with a saturated $NaHCO_3$ solution until basic. The water phase was extracted twice with 20 ml of dichloromethane. The organic layers were combined and dried with $MgSO_4$, filtered and evaporated to yield 1.15 g 2,3-dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]heptan-6-yl amine (yield 95%; liquid). The product obtained has a purity >95% and was used as such in the next step without any further purification.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.33 (3H, t, *J*= 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.16 (2H, br. s, NH_2), 2.44 (1H, dd, *J*= 13.4 Hz, *J*= 7.1 Hz, $C\underline{H}_{7a}H_{7b}$), 2.61 (1H, dt, *J*= 16.5 Hz, *J*= 2.5 Hz, $C\underline{H}_{4a}H_{4b}$), 2.80-2.93 (2H, m, $CH_{7a}\underline{H}_{7b}$ + $CH_{4a}\underline{H}_{4b}$), 3.20 (1H, br. q, *J*= 8.1 Hz, CH 1), 3.30-3.37 (1H, m, CH 5), 4.25 (2H, q, *J*= 7.1 Hz, $COOC\underline{H}_2CH_3$), 4.60 (1H, s, CHBr, 2), 4.72 (1H, br. d, *J*= 2.6 Hz, CHBr, 3). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.18 (CH_3), 34.23 (CH_2, 4), 39.35 (CH_2, 7), 43.67 (CH, 1), 49.22 (CH, 5), 55.24 ($C_{quat.}$), 56.48 (CHBr, 3), 60.02 (CHBr, 2), 61.40 ($COO\underline{C}H_2CH_3$), 175.77 (COOEt). **IR (cm^{-1}) ν_{max} :** 1729. **MS: m/z (%):** (GC) no M^+, 314/312/310 (M^+-Et, 11), 270/268/266 (36), 180 (26), 140 (38), 115 (100), 106 (34), 80 (34).

Ethyl 8-(endo)bromo-2azatricyclo[3.3.0.0^{3,6}]octan-3-yl carboxylate 447

1.12 g of ethyl (1*R**,2*S**,3*S**,5*R**,6*S**)-6-amino-2,3-dibromobicyclo[3.2.0]heptane-6-carboxylate was dissolved in 115 ml of dry THF and 0.36 g (1.1 equiv.) of triethylamine was added. The resulting solution was refluxed for 24h. The solution was concentrated up to 20% of its original volume and 50 ml of dry ether was added so that a white powder was formed that was filtered off. The filtrate was evaporated and the resulting oil was purified by flash chromatography and gave 0.68 g ethyl-8-(endo)bromo-2azatricyclo[3.3.0.0^{3,6}]octan-3-yl carboxylate. (solvent: CH_2Cl_2/EtOAc 1/1; R_f= 0.34; yield 80%; liquid) .

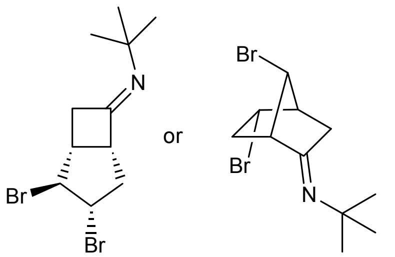


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.29 (3H, t, *J*= 7.3 Hz, $COOCH_2C\underline{H}_3$), 1.83 (1H, dd, *J*= 14.5 Hz, *J*= 7.6 Hz, $C\underline{H}_{7a}H_{7b}$), 1.92 (1H, d, *J*= 7.6 Hz, $C\underline{H}_{4a}H_{4b}$), 2.24 (1H, ddd, *J*= 14.4 Hz, *J*= 9.9 Hz, *J*= 4.6 Hz, $CH_{7a}C\underline{H}_{7b}$), 2.34 (1H, dd, *J*= 7.6 Hz, *J*= 2.6 Hz, $CH_{4a}C\underline{H}_{4b}$), 2.66 (1H, ddd, *J*= 2.6 Hz, *J*= 2.6 Hz, *J*= 1.6 Hz, CH 5), 2.70 (1H, dd, *J*= 4.6 Hz, *J*= 2.9 Hz, CH 6), 3.57 (1H, br. s, CH 1), 4.19 (2H, q, *J*= 7.2 Hz, $COOC\underline{H}_2CH_3$), 4.29 (1H, ddd, *J*= 9.8 Hz, *J*= 7.6 Hz, *J*= 1.6 Hz, CHBr 8). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 14.20 ($COOCH_2\underline{C}H_3$), 32.97 (CH_2, 7), 39.01 (CH_2, 4), 43.47 (CH, 5), 54.00 (CH, 6), 55.38 (CH, 8), 60.93 (CH_2, $COO\underline{C}H_2CH_3$), 63.18 (CH, 1), 70.26 ($C_{quat.}$, 3), 169.00 (C=O). **IR (cm^{-1}) ν_{max} :** 1732 (C=O). **MS: m/z (%):** 261/259 (M^+, 8), 194/192 (40), 180 (79), 106 (64), 99 (100).

6.14.2. Synthesis of *N*-[5,7-dibromobicyclo[2.2.1]hept-2-ylidene]-t-butylamine 454

Imine 449

0.5 g (1.9 mmol) of 2,3-dibromobicyclo[3.2.0]heptan-6-one was dissolved in 15 ml of dry diethyl ether. The solution was cooled to -78°C when 0.55 g (4 equiv.) of isopropylamine was added. At this temperature a solution of 0.21 g Ti(IV)Cl in 5 ml of pentane was added dropwise. The resulting suspension was stirred for 1h at -78°C. The reaction mixture was subsequently filtered over celite and extracted with diethyl ether and a 1N NaOH solution. The organic layer was dried with $MgSO_4$ for 10 minutes after which it was filtered and evaporated. This led to the isolation of 0.53 g of imine **449** (yield = 88 %; 80/20). This compound proved to be very unstable and had to be used immediately after its preparation. Storing this compound at room temperature for 15 minutes led to degradation products.



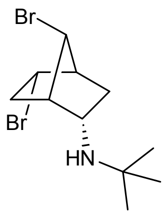
^{1}H-NMR (270 MHz, $CDCl_3$) δ: <u>MAJOR</u>, *MINOR*, not assigned: 1.26 (9H, s, t-Bu); 1.76-1.82 (1H, m, $C\underline{H}_aH_b$); 2.43-2.50 (1H, m, $C\underline{H}_cH_d$), 2.75-2.81 (2H, m, CH + CH), 2.85-2.96 (1H, m, $CH_a\underline{H}_b$), 3.09-3.15 (1H, m, $CH_c\underline{H}_d$), *4.15* (1H, br. s, CHBr), <u>4.24</u> (1H, br. s, CHBr), 4.72-4.79 (1H, m, CHBr). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** <u>MAJOR</u>, *MINOR*, not assigned: <u>29.67</u> (CH_3, t-Bu), *30.44* (CH_3, t-Bu), <u>37.16</u> (CH_2), *36.03*

(CH_2), $\underline{36.68}$ (CH_2), *36.39* (CH_2), $\underline{48.57}$ (CHBr), *48.05* (CHBr), $\underline{49.76}$ (CH), *49.99* (CH), $\underline{53.33}$ (CHBr), *53.80* (CHBr), *55.54* (CH), $\underline{55.87}$ (CH), 56.01 ($C_{quat.}$, t-Bu), $\underline{167.65}$ (C=N), *166.59* (C=N).

6.14.2.1. Reduction of imine 449

***N*-[5,7-dibromobicyclo[2.2.1]hept-2-ylidene]-t-butylamine 454**

0.06 g of $LiAlH_4$ (1.1 equiv.) was stirred in 1 ml of dry THF solution at 0°C under a nitrogen atmosphere. To this mixture a solution of 0.45 g of imine **449** in 8 ml of dry THF was slowly added. After the addition was completed the reaction mixture was heated under reflux for an overnight period. Water was added until gas evolution ceased. The mixture was filtered over celite and after evaporation of the solvent an oil was obtained which was purified by column chromatography. 0.12 g of pure compound (26 %) was obtained which proved to be rather stable.

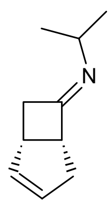


^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.07 (9H, s, t-Bu), 1.69 (1H, dd, *J*= 13.7 Hz, *J*= 4.8 Hz, $C\underline{H}_aH_b$), 2.08 (1H, ddd, *J*= 13.4 Hz, *J*= 4.6 Hz, *J*= 2.1 Hz, $CH_a\underline{H}_b$), 2.17 (1H, ddd, *J*= 17.4 Hz, *J*= 4.4 Hz, *J*= 2.1 Hz, $C\underline{H}_cH_d$), 2.27 (1H, br.s, CH), 2.45-2.46 (1H, m, CH), 2.49-2.56 (1H, m, $CH_c\underline{H}_d$), 3.17-3.24 (1H, m, CHNt-Bu), 4.08 (1H, s, CHBr), 4.75-4.82 (1H, m, CHBr). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 30.15 (CH_3, t-Bu), 30.58 (CH_2), 35.00 (CH_2), 50.08 (CH), 50.48 (CH), 50.80 ($C_{quat.}$, t-Bu), 50.85 (CH), 52.42 (CHBr), 55.08 (CHBr). **IR (cm^{-1}) ν_{max} :** 2966, 2867. **MS: m/z (%):** (ES, Pos) 328/326/324 (M^++H, 100). **Chromatography**: Hex/EtOAc R_f= 0.24.

6.14.3. Synthesis of N-[(1*S**,5*R**)-bicyclo[3.2.0]hept-2-en-6-ylidene]alkylamine

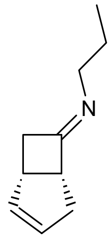
The same procedure as for the synthesis of N-[3-(chloromethyl)-1-cyclobutylidene]amines applies here. The bicyclo[3.2.0]hept-2-en-6-one is used as starting material and the corresponding amines were used to make the imines. The N-(bicyclo[3.2.0]hept-2-en-6-ylidene)alkylamines were obtained as oils.

N-[(1*S,5*R**)-Bicyclo[3.2.0]hept-2-en-6-ylidene]-isoprpylamine 456a**



^{1}H-NMR (270 MHz, $CDCl_3$) δ: $\underline{\text{MAJOR}}$, *MINOR*, not assigned: $\underline{1.06}$ (3H, d, *J*= 6.3 Hz, $NCH(C\underline{H}_3)_2$), $\underline{1.10}$ (3H, d, *J*= 6.3 Hz, $NCH(C\underline{H}_3)_2$), *1.11* (3H, d, *J*= 6.3 Hz, $NCH(C\underline{H}_3)_2$), *1.15* (3H, d, *J*= 6.3 Hz, $NCH(C\underline{H}_3)_2$), 2.50-2.64 (3H, m, CH_2 4 +$C\underline{H}_{7a}H_{7b}$), 3.01 (1H, dd, *J*= 16.2 Hz, *J*= 8.3 Hz, $CH_{7a}\underline{H}_{7b}$), *3.09* (1H, ddd, *J*= 16.8 Hz, *J*= 8.6 Hz, *J*= 1.3 Hz, CH_2 7), $\underline{3.27\text{-}3.38}$ (1H, m, CH 1), $\underline{3.36}$ (1H, sept, *J*= 6.3 Hz, $NC\underline{H}(CH_3)_2$), *3.62* (1H, qq, *J*= 6.3 Hz, *J*= 6.3 Hz, $NC\underline{H}(CH_3)_2$), $\underline{3.66\text{-}3.74}$ (1H, CH 5), $\underline{5.78}$ (2H, br. s, CH=). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 23.58 ($NCH(\underline{C}H_3)_2$), 23.90 ($NCH(\underline{C}H_3)_2$), 37.20 (CH_2 4), 39.71 (CH 1), 41.06 (CH_2 7), 51.54 (CH 5 or $N\underline{C}H$), 51.93 ($N\underline{C}H$ or CH 5), 132.00 (CH=), 132.08 (CH=), 173.12 (C=N). MINOR: 22.67 ($NCH(\underline{C}H_3)_2$), 22.73 ($NCH(\underline{C}H_3)_2$), 37.09 (CH_2 4), 39.17 (CH 1), 44.76 (CH_2 7), 49.22 (CH 5 or NCH), 50.24 (NCH or CH 5), 130.65 (CH=), 133.28 (CH=), 171.48 (C=N). **IR (cm^{-1}) ν_{max} :** 1706 (C=N), **MS: m/z (%):** (direct inlet) 149 (M^+, 3), 107 (11), 83 (46), 80 (20), 79 (34), 67 (20), 66 (100). Yield = 95 % (63/37).

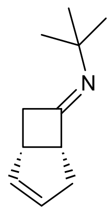
N-[(1*S,5*R**)-Bicyclo[3.2.0]hept-2-en-6-ylidene]-1-propanamine 456b**



^{1}H-NMR (270 MHz, $CDCl_3$) δ: $\underline{\text{MAJOR}}$, *MINOR*, not assigned: $\underline{0.88}$ (3H, t, *J*= 7.4 Hz, $NCH_2CH_2C\underline{H}_3$), *0.94* (3H, t, *J*= 7.4 Hz, $NCH_2CH_2C\underline{H}_3$), $\underline{1.60}$ (2H, sext., *J*= 7.5 Hz, $NCH_2C\underline{H}_2CH_3$), $\underline{2.50\text{-}2.59}$ (1H, m, $C\underline{H}_{4a}H_{4b}$), $\underline{2.50\text{-}2.60}$ (1H, m, $C\underline{H}_{7a}H_{7b}$), $\underline{2.65\text{-}2.71}$ (1H, m, $CH_{4a}\underline{H}_{4b}$), $\underline{2.99}$ (1H, dd, *J*= 16.3 Hz, *J*= 8.4 Hz, $CH_{7a}\underline{H}_{7b}$), $\underline{3.13}$ (2H, t, *J*= 6.6 Hz, $NC\underline{H}_2CH_2CH_3$), $\underline{3.30\text{-}3.40}$ (1H, m, CH 1), $\underline{3.66\text{-}3.76}$ (1H, m, CH 5), $\underline{5.80}$ (2H, br. s, 2 x CH=). Some minor peaks overlap and couldn't be assigned. **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 11.91 ($NCH_2CH_2\underline{C}H_3$), 23.76 ($NCH_2\underline{C}H_2CH_3$), 37.18 ($CH_2$ 4), 39.68 (CH 1), 41.44 (CH_2 7), 52.08 (CH 5), 53.58 ($N\underline{C}H_2CH_2CH_3$), 131.95 (CH=), 133.12 (CH=), 175.25 (C=N); MINOR: 12.06 ($NCH_2CH_2\underline{C}H_3$), 24.12 ($NCH_2\underline{C}H_2CH_3$), 36.33 ($CH_2$ 4), 39.08 (CH 1), 44.82 (CH_2 7), 49.38 (CH 5), 54.27 ($N\underline{C}H_2CH_2CH_3$), 130.67 (CH=), 133.01 (CH=), 173.72 (C=N). **IR (cm^{-1}) ν_{max} :** 1709. **MS: m/z (%):** (direct inlet) 149 (M^+, 4), 107 (4), 83 (29), 80 (13), 79 (38), 77 (13), 66 (100), 65 (9), 40 (51). Yield = 95 % (76/24).

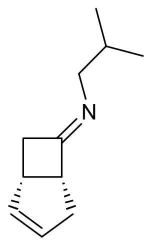
***N*-[(1*S**,5*R**)-Bicyclo[3.2.0]hept-2-en-6-ylidene]t-butylamine 456c**

Only the spectra of the major isomer are given.



^{1}H-NMR (270 MHz, $CDCl_3$) δ: MAJOR: 1.18 (9H, s, t-Bu), 2.53-2.63 (2H, m, CH_2 4), 2.73 (1H, dt, *J*= 15.9 Hz, *J*= 2.9 Hz, $C\underline{H}_{7a}H_{7b}$), 3.16-3.28 (1H, m, $CH_{7a}\underline{H}_{7b}$), 3.25-3.35 (1H, m, CH 1), 3.65-3.75 (1H, m, CH 5), 5.78 (2H, br. s, CH=), **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 30.04 (t-Bu), 37.70 (CH_2 4), 40.25 (CH 1), 45.48 (CH_2 7), 53.78 (CH 5), 56.14 ($C_{quat.}$, t-Bu), 132.20 (CH=), 133.26 (CH=), 172.11 (C=N). **IR (cm^{-1}) ν_{max} :** 1704. **MS: m/z (%):** (GC) 163 (M^+, 2), 107 (10), 66 (25), 57 (100). Yield = 84 % (94/6).

N-[(1*S,5*R**)-Bicyclo[3.2.0]hept-2-en-6-ylidene]isobutylamine 456d**



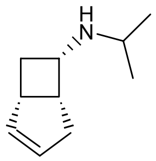
^{1}H-NMR (270 MHz, $CDCl_3$) δ: $\underline{\text{MAJOR}}$, *MINOR*, not assigned: $\underline{0.88}$ (6H, d, *J*= 6.6 Hz, $NCH_2CH(C\underline{H}_3)_2$), *0.92* (3H, d, *J*= 7.3 Hz, $NCH_2CH(C\underline{H}_3)_2$), *0.95* (3H, d, *J*= 6.9 Hz, sept., *J*= 6.6 Hz, $NCH_2CH(C\underline{H}_3)_2$), 1.89 (1H, sept., *J*= 6.6 Hz, $NCH_2C\underline{H}(CH_3)_2$), $\underline{2.49\text{-}2.75}$ (1H, m, $C\underline{H}_{4a}H_{4b}$), *2.56-2.60* (1H, m, $C\underline{H}_{4a}H_{4b}$), $\underline{2.55\text{-}2.60}$ (1H, m, $C\underline{H}_{7a}H_{7b}$), 2.61-2.75 (1H, m, $CH_{4a}\underline{H}_{4b}$), 2.97 (1H, dd, *J*= 15.5 Hz, *J*= 8.6 Hz, $CH_{7a}\underline{H}_{7b}$), 2.98 (2H, d, *J*= 6.6 Hz, $NC\underline{H}_2CH(CH_3)_2$), 3.30-3.38 (1H, m, CH 1), 3.70-3.77 (1H, m, CH 5), 5.78 (2H, br. s, CH=). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** MAJOR: 20.65 ($NCH_2CH(\underline{C}H_3)_2$), 20.68 ($NCH_2CH(\underline{C}H_3)_2$), 29.47 ($NCH_2\underline{C}H(CH_3)_2$), 37.25 ($CH_2$ 4), 39.60 (CH 1), 41.62 (CH_2 7), 52.08 (CH 5), 59.86 ($N\underline{C}H_2CH(CH_3)_2$), 132.02 (CH=), 133.13 (CH=), 175.29 (C=N); MINOR: 20.79 ($NCH_2CH(\underline{C}H_3)_2$), 20.88 ($NCH_2CH(\underline{C}H_3)_2$), 29.69 ($NCH_2\underline{C}H(CH_3)_2$), 36.24 ($CH_2$ 4), 38.99 (CH 1), 44.91 (CH_2 7), 49.42 (CH 5), 60.22

($N\underline{C}H_2CH(CH_3)_2$), 130.67 (CH=), 133.20 (CH=), 175.18 (C=N). **IR (cm^{-1}) ν_{max} :** 1709. **MS: m/z (%):** (direct inlet) 163 (M^+, 5), 107 (10), 91 (12), 86 (64), 84 (100), 66 (88), 57 (97). Yield = 89 % (79/21).

6.14.3.1. Reduction of N-[(1*S**,5*R**)-bicyclo[3.2.0]hept-2-en-6-ylidene]-1-alkylamines

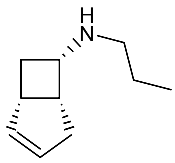
A general protocol is given as an example. In an oven-dried flask of 100 ml, 0.46 g $LiALH_4$ (1.5 equiv.) was stirred in 10 ml of dry diethyl ether at 0°C and under a N_2-atmosphere. A solution of 1.25 g N-[(1*S**,5*R**)--bicyclo[3.2.0]hept-2-en-6-ylidene]-t-butylamine (1 equiv.) in 20 ml of dry ether was added dropwise at this temperature. The suspension was stirred overnight at room temperature and some drops of water were added until the gas evolution ceased. The mixture was filtered over a mixture of $MgSO_4$ and celite (1/1) and washed thoroughly with dry dichloromethane. The filtrate was evaporated and 1.19 g of N-(t-butyl)bicyclo[3.2.0]hept-2-en-6-amine was obtained as an oil (yield = 94 %). The two diastereoisomers were separated by column chromatography and the major isomer was obtained in 84 % yield. The minor isomer was isolated in 3 % yield.

(1*S, 5*R**, 6*S**)-N-Isopropylbicyclo[3.2.0]hept-2-en-6-amine 458a**



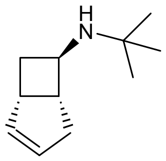
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.00 (3H, d, *J*= 5.9 Hz, CH_3), 1.02 (3H, d, *J*= 6.27 Hz, CH_3), 1.34 (1H, dddd, *J*= 12.5 Hz, *J*= 6.5 Hz, *J*= 5.4 Hz, *J*= 0.7 Hz, $C\underline{H}_{7a}H_{7b}$), 2.44-2.50 (2H, m, $C\underline{H}_{4a}\underline{H}_{4b}$), 2.57-2.66 (1H, m, $CH_{7a}\underline{H}_{7b}$), 2.68 (1H, sept, *J*= 6.3 Hz, $NC\underline{H}(CH_3)_2$), 2.97-3.05 (1H, m, CH, 1), 3.05-3.16 (1H, m, CH, 5), 3.59 (1H, td, *J*= 8.0 Hz, *J*= 8.1 Hz, NCH, 6), 5.78 (2H, br. s, CH=CH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 22.70 (CH_3), 23.36 (CH_3), 32.04 (CH_2, 4), 38.22 (CH_2, 7), 40.47 (CH, 1), 40.92 (CH, 5), 46.34 ($NHC\underline{H}(CH_3)_2$), 49.72 (CH, 6), 131.84 (CH=), 135.70 (CH=). **IR (cm^{-1}) ν_{max} :** 2963. **MS: m/z (%):** (GC) no M^+, 136 (M^+-CH_3, 25), 85 (100), 70 (90). **Chromatography:** EtOAc/MeOH/NEt_3 98/1/1 R_f= 0.27. Yield = 53 %.

(1*S, 5*R**, 6*S**)-N-Propylbicyclo[3.2.0]hept-2-en-6-amine 458b**



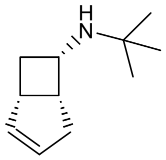
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.91 (3H, t, *J*= 7.4 Hz, $NHCH_2CH_2C\underline{H}_3$), 1.33-1.41 (1H, m, $C\underline{H}_{7a}H_{7b}$), 1.48 (2H, hex, *J*= 7.4 Hz, $NHCH_2C\underline{H}_2CH_3$), 2.41 (2H, t, *J*= 7.4 Hz, $NHC\underline{H}_2CH_2CH_3$), 2.42-2.49 (2H, m, CH_2, 4), 2.61 (1H, dddd, *J*= 12.3 Hz, *J*= 9.0 Hz, 7.9 Hz, *J*= 1.7 Hz, $CH_{7a}\underline{H}_{7b}$), 3.01-3.09 (1H, m, CH, 1), 3.10-3.16 (1H, m, CH, 5), 3.41-3.51 (1H, m, CH, 6), 5.79 (2H, s, CH=CH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 11.99 (CH_3, $NHCH_2CH_2\underline{C}H_3$), 23.47 ($CH_2$, $NHCH_2\underline{C}H_2CH_3$), 31.90 ($CH_2$, 4), 37.54 ($CH_2$, 7), 40.36 (CH, 5), 40.75 (CH, 1), 49.83 ($NH\underline{C}H_2CH_2CH_3$), 52.54 (CH, 6), 131.84 (CH=), 135.69 (CH=). **IR (cm^{-1}) ν_{max} :** 3303 (br.), 2957 (br.). **MS: m/z (%):** (GC) 151 (M^+, 2), 150 (M^+-1, 5), 136 (8), 122 (13), 108 (7), 91 (26), 85 (84), 70 (77), 57 (16), 56 (100). **Chromatography**: EtOAc/MeOH 96/4 R_f= 0.09. Yield = 44 %.

(1S^*, 5R^*, 6R^*)-N-(t-butyl)bicyclo[3.2.0]hept-2-en-6-amine 459c



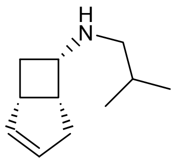
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.07 (9H, s, t-Bu), 1.89 (1H, ddd, *J*= 11.5 Hz, *J*= 8.6 Hz, *J*= 8.6 Hz, C$\underline{H}_{7a}$H$_{7b}$), 2.15-2.23 (1H, m, CH$_{7a}\underline{H}_{7b}$), 2.25-2.36 (1H, m, C$\underline{H}_{4a}$H$_{4b}$), 2.50-2.56 (1H, m, CH$_{4a}\underline{H}_{4b}$), 2.57-2.63 (1H, m, CH 5), 3.05-3.13 (2H, m, 2 x CH 6, CH 1), 5.71-5.73 (1H, m, CH=), 5.77-5.81 (1H, m, CH=). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 30.01 (CH$_3$, t-Bu), 39.03 (CH$_2$, 7), 39.19 (CH$_2$, 4), 40.16 (CH, 1), 47.74 (CH, 5), 50.76 (C$_{quat.}$, tBu), 54.54 (CH, 6), 130.53 (CH=), 134.61 (CH=). IR (cm^{-1}) ν_{max} : 3048 (CH=). **MS: m/z (%):** (GC) 165 (M$^+$, 3), 150 (M$^+$-CH$_3$, 15), 108 (17), 99 (71), 94 (31), 84 (100), 57 (21), 43 (39). **Chromatography:** EtOAc/MeOH/NEt$_3$ 96/3/1 R$_f$= 0.13. Yield = 3 %.

(1S^*, 5R^*, 6S^*)-N-(t-butyl)bicyclo[3.2.0]hept-2-en-6-amine 458c



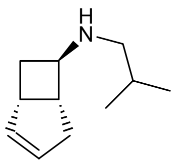
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.05 (9H, s, t-Bu), 1.23-1.41 (1H, m, C$\underline{H}_{7a}$H$_{7b}$), 2.39 (1H, dd, *J*= 17.5 Hz, *J*= 10.2 Hz, C$\underline{H}_{4a}$H$_{4b}$), 2.59-2.71 (2H, m, CH$_{4a}\underline{H}_{4b}$, CH$_{7a}\underline{H}_{7b}$), 2.89-2.97 (1H, m, CH, 1), 3.06-3.16 (1H, m, CH, 5), 3.68 (1H, ddd, *J*= 8.6 Hz, *J*= 8.4 Hz, *J*= 8.4 Hz, CH, 6), 5.78 (2H, s, C$\underline{H}$=C$\underline{H}$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 29.96 (CH$_3$, t-Bu), 32.13 (CH$_2$, 4), 40.16 (CH, 1), 41.11 (CH$_2$, 7), 43.81 (CH, 5), 46.56 (CH, 6), 50.51 (C$_{quat.}$), 132.00 (CH=), 135.45 (CH=). **IR (cm^{-1}) ν_{max} :** 3048 (CH=), 1606 (CH=). **MS: m/z (%):** (GC) 165 (M$^+$, 4), 150 (12), 108 (15), 99 (73), 94 (25), 84 (100), 57 (27), 43 (36). **Chromatography:** EtOAc/MeOH/NEt$_3$ 96/3/1 R$_f$= 0.34. Yield = 84 %.

(1S^*, 5R^*, 6S^*)-N-isobutylbicyclo[3.2.0]hept-2-en-6-amine 458d



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 0.90 (3H, d, *J*= 6.6 Hz, CH$_3$), 0.91 (3H, d, *J*= 6.6 Hz, CH$_3$), 1.33-1.41 (1H, m, C$\underline{H}_{7a}$H$_{7b}$), 1.70 (1H, sept, *J*= 6.6 Hz, NCH$_2$C$\underline{H}$(CH$_3$)$_2$), 2.26 (2H, d, *J*= 6.6 Hz, NC$\underline{H}_2$CH(CH$_3$)$_2$), 2.36-2.50 (2H, m, CH$_2$, 4), 2.54-2.67 (1H, m, CH$_{7a}\underline{H}_{7b}$), 3.03-3.18 (2H, m, CH 1, CH 5), 3.39-3.49 (1H, m, CH, 6), 5.79 (2H, br. s, C$\underline{H}$=C$\underline{H}$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 20.83 (CH$_3$), 20.90 (CH$_3$), 28.72 (NCH$_2\underline{C}$H(CH$_3$)$_2$), 31.82 (CH$_2$, 4), 37.43 (CH$_2$, 7), 40.31 (CH, 5), 40.66 (CH, 1), 52.61 (CH, 6), 55.90 (N$\underline{C}$H$_2$CH(CH$_3$)$_2$), 131.86 ($\underline{C}$H=), 135.65 ($\underline{C}$H=). **IR (cm^{-1}) ν_{max} :** 2954 (br.). **MS: m/z (%):** (GC) 165 (M$^+$, 3), 164 (M$^+$-1, 2), 150 (3), 122 (23), 99 (65), 91 (26), 84 (37), 56 (100), 44 (32). **Chromatography**: EtOAc/Hex 90/10 R$_f$= 0.3. Yield = 66 %.

(1S^*, 5R^*, 6R^*)-N-isobutylbicyclo[3.2.0]hept-2-en-6-amine 459d



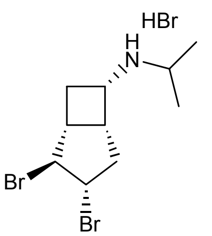
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 0.91 (6H, d, *J*= 6.6 Hz, CH$_3$), 1.71 (1H, sept, *J*= 6.6 Hz, NCH$_2$C$\underline{H}$(CH$_3$)$_2$), 1.89 (1H, ddd, *J*= 11.6 Hz, 8.4 Hz, *J*= 8.4 Hz, C$\underline{H}_{7a}$H$_{7b}$), 2.13 (1H, ddd, *J*= 11.5 Hz, *J*= 7.8 Hz, *J*= 2.7 Hz, CH$_{7a}\underline{H}_{7b}$), 2.23-2.40 (3H, m, C$\underline{H}_{4a}$H$_{4b}$ + NC$\underline{H}_2$CH(CH$_3$)$_2$), 2.55-2.61 (2H, m, CH 5 + CH$_{4a}\underline{H}_{4b}$), 2.90-2.98 (1H, m, CH 6), 3.10-3.16 (1H, m, CH 1), 5.69-5.72 (1H, m, CH=), 5.78-5.82 (1H, m, CH=). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 20.81 (CH$_3$), 28.54 (NCH$_2\underline{C}$H(CH$_3$)$_2$), 35.56 (CH$_2$, 7), 39.42 (CH$_2$, 4), 40.09 (CH, 1), 45.48 (CH, 5), 55.35 (N$\underline{C}$H$_2$CH(CH$_3$)$_2$), 60.25 (N$\underline{C}$H, 6), 130.55 (CH=), 134.59 (CH=). **IR**

(cm^{-1}) ν_{max} : 3295 (br.), 2954 (br.). **MS: m/z (%):** (GC) 165 (M^+, 3), 164 (M^+-1, 3), 150 (6), 122 (25), 99 (63), 93 (26), 91 (30), 84 (35), 56 (100), 44 (37). **Chromatography**: EtOAc/Hex 90/10 R_f= 0.1. Yield = 6 %.

6.14.3.2. Bromination of (1*S**, 5*R**, 6*S**)-N-alkylbicyclo[3.2.0]hept-2-en-6-amines.

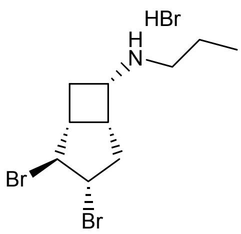
A solution of 3.3 mmol (1*S**, 5*R**, 6*S**)-N-alkylbicyclo[3.2.0]hept-2-en-6-amine was dissolved in 5 ml of dry dichloromethane and cooled to 0°C in an ice bath. A concentrated hydrobromic acid solution (1.02 equiv.; 3.96 mmol; 48% HBr in H_2O) was added and the mixture was stirred vigorously during 15 minutes. After this time, 3.96 mmol (1.02 equiv.) of bromine dissolved in a small amount of dichloromethane was added and the reaction was allowed to warm to room temperature overnight. During this period a white powder is formed and 10 ml of dry ether was added to improve the yield of the formed salt. The suspension was filtered and the powder was washed thoroughly with dry diethyl ether. This powder is the hydrobromic salt of the brominated product and was dried under high vacuum. These salts are only slightly hygroscopic and are very stable in a closed vessel when stored at room temperature. The free amine can be generated form these salts by dissolving them in a saturated $NaHCO_3$ solution and performing an extraction with dichloromethane. The organic layer was dried with $MgSO_4$ overnight. The $MgSO_4$ was filtered off and after evaporation of the solvent an oil was obtained which was the pure (1*R**,2*S**,3*S**,5*R**,6*S**)-2,3-dibromo-N-(alkyl)-bicyclo[3.2.0]heptan-6-amine. These compounds are less stable and should be used preferably on the day of preparation.

(1*R**,2*S**,3*S**,5*R**,6*S**)-2,3-Dibromo-N-isopropylbicyclo[3.2.0]heptan-6-amine hydrobromide 461a



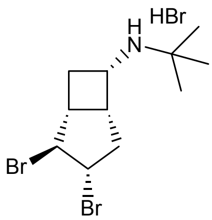
^{1}H-NMR (270 MHz, CD_3OD) δ: 1.32 (3H, d, *J*= 6.6 Hz, CH_3), 1.34 (3H, d, *J*= 6.6 Hz, CH_3), 2.35-2.53 (2H, m, $C\underline{H}_{7a}H_{7b}$, $C\underline{H}_{4a}H_{4b}$), 2.56-2.67 (1H, m, $CH_{4a}\underline{H}_{4b}$), 2.83-2.99 (2H, m, $CH_{7a}\underline{H}_{7b}$, CH), 3.23-3.32 (1H, m, CH), 3.37 (1H, sept, *J*= 6.6 Hz, $NC\underline{H}(CH_3)_2$), 3.94-4.03 (1H, m, CH, 6), 4.24-4.37 (2H, m, 2xCHBr). **^{13}C-NMR (68 MHz, CD_3OD) δ:** 19.23 (CH_3), 19.86 (CH_3), 35.00 (CH_2), 36.32 (CH_2), 43.04 (CH), 43.90 (CH), 47.96 (CH), 51.72 (CH), 56.53 (CHBr), 60.56 (CHBr). **IR (cm^{-1}) ν_{max}** (KBr): 3436 (br.), 2924 (br.). **MS: m/z (%):** (ES, Pos) 314/312/310 (M^+, 100). **Mp=** 182.3-182.9 (degradation). Yield = 95 %.

(1R^*,2S^*,3S^*,5R^*,6S^*)-2,3-Dibromo-N-propylbicyclo[3.2.0]heptan-6-amine hydrobromide 461b



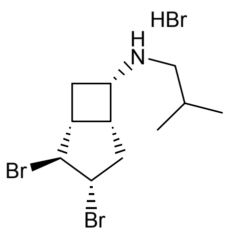
^{1}H-NMR (270 MHz, CD_3OD) δ: 1.02 (3H, t, *J*= 7.4 Hz, $NCH_2CH_2C\underline{H}_3$), 1.72 (2H, hex, *J*= 7.4 Hz, $NCH_2C\underline{H}_2CH_3$), 2.33-2.52 (2H, m, $C\underline{H}_{4a}H_{4b}$ + $C\underline{H}_{7a}H_{7b}$), 2.64 (1H, ddd, *J*= 13.7 Hz, *J*= 8.4 Hz, *J*= 6.4 Hz, $CH_{4a}\underline{H}_b$), 2.81 (4H, m, $CH_{7a}\underline{H}_{7b}$, CH, $NC\underline{H}_2CH_2CH_3$), 3.19-3.28 (1H, m, CH), 3.30-3.22 (1H, m, CH), 3.85-3.94 (1H, m, CH), 4.25-4.38 (2H, m, 2x CHBr). **^{13}C-NMR (68 MHz, CD_3OD) δ:** 11.32 ($NCH_2CH_2\underline{C}H_3$), 20.52 ($NCH_2\underline{C}H_2CH_3$), 33.84 ($CH_2$), 36.05 ($CH_2$), 42.41 (CH), 43.47 (CH), (CH 6 and $N\underline{C}H_2CH_2CH_3$ overlap with CD_3OD), 56.51 (CHBr), 60.56 (CHBr). **IR (cm^{-1}) ν_{max} :** 3430 (br.), 2903 (br.). **MS: m/z (%):** (ES, Pos) 314/312/310 (M^++1, 100), **Mp:** 156.1-158.5 (degradation temperature). Yield = 76 %.

(1R^*,2S^*,3S^*,5R^*,6S^*)-2,3-Dibromo-N-(t-butyl)-bicyclo[3.2.0]heptan-6-amine hydrobromide 461c



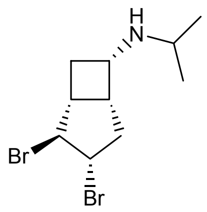
^{1}H-NMR (270 MHz, DMSO) δ: 1.26 (9H, s, tBu), 2.34-2.47 (2H, m, $C\underline{H}_{4a}H_{4b}$, $C\underline{H}_{7a}H_{7b}$), 2.55-2.69 (1H, m, CH), 2.73-2.81 (2H, m, $CH_{4a}\underline{H}_{4b}$, $CH_{7a}\underline{H}_{7b}$), 3.09-3.16 (1H, m, CH), 3.92-3.97 (1H, m, CH), 4.29-4.36 (2H, m, 2 x CHBr), 8.56-8.64 (2H, m, $NH_2^+Br^-$). **^{13}C-NMR (68 MHz, DMSO) δ:** 25.43 (CH_3, t-Bu), 34.86 (CH_2), 34.95 (CH_2), 41.81 (CH), 41.90 (CH), 43.20 (CH), 56.37 (CHBr), 57.29 ($C_{quat.}$), 60.52 (CHBr). **IR (cm^{-1}) ν_{max} :** 2765 (br.), 3430 (br.). **MS: m/z (%):** (ES, Pos) 328/326/324 (M^+, 100). **Mp =** 197.1-200°C (degradation). Yield = 80 %.

(1R^*,2S^*,3S^*,5R^*,6S^*)-2,3-Dibromo-N-isobutylbicyclo[3.2.0]heptan-6-amine hydrobromide 461d



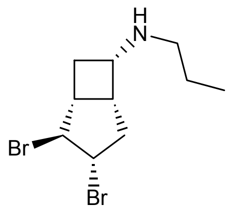
^{1}H-NMR (270 MHz, DMSO) δ: 0.94 (3H, d, *J*= 6.3 Hz, CH_3), 0.96 (3H, d, *J*= 6.3 Hz, CH_3), 1.97 (1H, non, *J*= 6.6 Hz, $NCH_2C\underline{H}(CH_3)_2$), 2.37-2.79 (7H, m, CH_2, CH_2, NCH_2, CH), 3.05-3.10 (1H, m, CH), 3.75-3.81 (1H, m, CH), 4.31-4.34 (2H, m, 2xCHBr). **^{13}C-NMR (68 MHz, DMSO) δ:** 19.91 (CH_3), 20.05 (CH_3), 25.18 ($NCH_2\underline{C}H(CH_3)_2$), 32.22 ($CH_2$), 33.94 ($CH_2$), 40.16 (CH), 40.65 (CH), 48.27 (CH), 51.91 (NCH_2), 56.24 (CHBr), 60.54 (CHBr). **IR (cm^{-1}) ν_{max} :** 3427 (br.). **MS: m/z (%):** (ES, Pos) 328/326/324 (M^++H, 100). **Mp.:** 167-168 °C (degradation). Yield = 81 %.

$1R^*,2S^*,3S^*,5R^*,6S^*$)-2,3-Dibromo-N-isopropyl[3.2.0]heptan-6-amine 465a



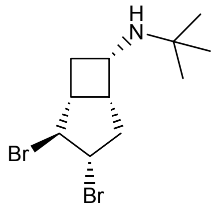
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.03 (3H, d, *J*= 6.3 Hz, CH_3), 1.05 (3H, d, *J*= 6.3 Hz, CH_3), 1.94 (1H, br. s, NH), 2.21 (1H, ddd, *J*= 12.8 Hz, *J*= 8.0 Hz, *J*= 8.0 Hz, $C\underline{H}_{7a}H_{7b}$), 2.33 (1H, ddd, *J*= 16.0 Hz, *J*= 3.5 Hz, *J*= 3.5 Hz, $C\underline{H}_{4a}H_{4b}$), 2.56-2.85 (3H, m, $CH_{7a}\underline{H}_{7b}$, $CH_{4a}\underline{H}_{4b}$, $NHC\underline{H}(CH_3)_2$), 2.98 (1H, ddd, *J*= 8.3 Hz, *J*= 8.3 Hz, *J*= 7.6 Hz, CH, 1), 3.25-3.36 (1H, m, CH 5), 3.47 (1H, ddd, *J*= 8.6 Hz, *J*= 8.4 Hz, *J*= 8.4 Hz, CH 6), 4.49 (1H, s, CHBr), 4.66-4.71 (1H, m, CHBr). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 22.77 (CH_3), 23.40 (CH_3), 34.41 (CH_2, 4), 35.94 (CH_2, 7), 44.06 (CH, 1), 45.25 (CH, 5), 46.00 ($NH\underline{C}H(CH_3)_2$), 46.59 (CH, 6), 57.34 (CHBr, 3), 60.77 (CHBr, 2). **IR (cm^{-1}) ν_{max} :** 2818. **MS: m/z (%):** (ES, Pos) 314/312/310 (M^++1, 100).

($1R^*,2S^*,3S^*,5R^*,6S^*$)-2,3-Dibromo-N-propyl[3.2.0]heptan-6-amine 465b



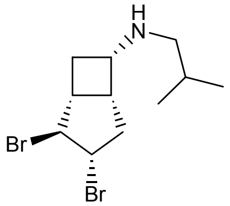
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J*= 7.4 Hz, $NHCH_2CH_2C\underline{H}_3$), 1.50 (2H, hex, *J*= 7.4 Hz, $NHCH_2C\underline{H}_2CH_3$), 2.21 (1H, ddd, *J*= 13.0 Hz, *J*= 7.4 Hz, *J*= 7.3 Hz, $C\underline{H}_{7a}H_{7b}$), 2.33 (1H, ddd, *J*= 16.2 Hz, *J*= 3.1 Hz, *J*= 3.1 Hz, $C\underline{H}_{4a}H_{4b}$), 2.45 (2H, t, *J*= 7.3 Hz, $NHC\underline{H}_2CH_2CH_3$), 2.55-2.68 (1H, m, $CH_{7a}\underline{H}_{7b}$), 2.78 (1H, ddd, *J*= 16.4 Hz, *J*= 8.5 Hz, *J*= 7.9 Hz, $CH_{4a}\underline{H}_{4b}$), 2.94-3.03 (1H, m, CH, 1), 3.28-3.41 (2H, m, CH 5 + CH 6), 4.50 (1H, s, CHBr, 2), 4.67-4.71 (1H, m, CHBr, 3). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 11.93 ($NHCH_2CH_2\underline{C}H_3$), 23.20 ($NHCH_2\underline{C}H_2CH_3$), 34.20 ($CH_2$, 4), 35.33 ($CH_2$, 7), 43.97 (CH, 1), 44.64 (CH, 5), 48.88 ($NH\underline{C}H_2CH_2CH_3$), 49.09 (CH, 6), 57.30 (CHBr, 3), 66.81 (CHBr, 2), **IR (cm^{-1}) ν_{max} :** 2957 (br.). **MS: m/z (%):** (ES, Pos) 314/312/310 (M^++1, 100).

($1R^*,2S^*,3S^*,5R^*,6S^*$)-2,3-Dibromo-N-(t-butyl)-bicyclo[3.2.0]heptan-6-amine 465c



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.07 (9H, s, t-Bu), 1.69 (1H, br. s, NH), 2.20 (1H, ddd, *J*= 12.6 Hz, 8.2 Hz, *J*= 8.2 Hz, $C\underline{H}_{7a}H_{7b}$), 2.44 (1H, ddd, *J*= 15.9 Hz, *J*= 4.2 Hz, *J*= 4.2 Hz, $C\underline{H}_{4a}H_{4b}$), 2.58-2.78 (2H, m, $CH_{7a}\underline{H}_{7b}$, $CH_{4a}\underline{H}_{4b}$), 2.92 (1H, ddd, *J*= 8.2 Hz, *J*= 8.2 Hz, *J*= 7.8 Hz, CH, 5), 3.23-3.25 (1H, m, CH, 1), 3.51 (1H, ddd, *J*= 8.4 Hz, *J*= 8.3 Hz, *J*= 8.3 Hz, CH, 6), 4.44 (1H, d, *J*= 0.7 Hz, CHBr, 2), 4.61-4.66 (1H, m, CHBr, 3). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 29.88 (CH_3, t-Bu), 34.70 (CH_2, 4), 38.56 (CH_2, 7), 43.95 (CH, 1), 44.13 (CH, 5), 47.26 (CH, 6), 50.91 ($C_{quat.}$, t-Bu), 57.11 (CHBr, 3), 61.01 (CHBr, 2). **IR (cm^{-1}) ν_{max} :** 2964 (NH). **MS: m/z (%):** (ES, Pos) 328/326/324 (100), 272/270/268 (M^+-tBu, 20).

($1R^*$,$2S^*$,$3S^*$,$5R^*$,$6S^*$)-2,3-Dibromo-N-isobutyl[3.2.0]heptan-6-amine 465d



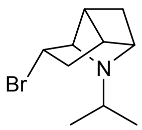
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 0.92 (3H, d, *J*= 6.6 Hz, CH_3), 0.94 (3H, d, *J*= 6.6 Hz, CH_3), 1.74 (1H, non, *J*= 6.6 Hz, $NCH_2C\underline{H}(CH_3)_2$), 2.17-2.40 (4H, m, $C\underline{H}_{4a}H_{4b}$, $C\underline{H}_{7a}H_{7b}$, $NC\underline{H}_2CH(CH_3)_2$), 2.56-2.68 (1H, m, $CH_{7a}\underline{H}_{7b}$), 2.80 (1H, ddd, *J*= 16.2 Hz, *J*= 8.9 Hz, *J*= 7.4 Hz, $CH_{4a}\underline{H}_{4b}$), 2.95-3.03 (1H, m, CH 1), 3.25-3.41 (2H, m, CH 5 + CH 6), 4.50 (1H, s, CHBr, 2), 4.67-4.71 (1H, m, CHBr, 3). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 20.79 (CH_3), 20.90 (CH_3), 28.54 ($NCH_2\underline{C}H(CH_3)_2$), 34.16 ($CH_2$, 4), 35.15 ($CH_2$, 7), 44.02 (CH, 1), 44.55 (CH, 5), 49.29 (CH, 6), 55.02 ($N\underline{C}H_2CH(CH_3)_2$), 57.38 (CHBr, 3), 60.70 (CHBr, 2). **IR (cm^{-1}) ν_{max} :** 2955. **MS: m/z (%):** (ES, Pos) 328/326/324 (M^++H, 100).

6.14.3.3. Ring closure of ($1R^*$,$2S^*$,$3S^*$,$5R^*$,$6S^*$)-2,3-dibromo-N-alkyl[3.2.0]heptan-6-amines

Two possible procedures can be used. In the first one the ($1R^*$,$2S^*$,$3S^*$,$5R^*$,$6S^*$)-2,3-dibromo-N-alkylbicyclo[3.2.0]heptan-6-amine hydrobromide (0.64 mmol) was dissolved in 25 ml of acetonitrile and 1.28 mmol (2 equiv.) of triethyl amine was added at room temperature. After adding these reagents, the reaction was heated under reflux overnight. The mixture was washed with a saturated $NaHCO_3$ solution and extracted with dichloromethane. After drying the organic phase with $MgSO_4$, the solution was filtered and the solvent was removed under reduced pressure. The 8-(endo)bromo-N-alkyl-2-azatricyclo[3.3.0.0^{3,6}]octanes were obtained as almost pure compounds. All products isolated were liquid oils.

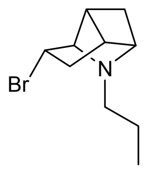
In the second procedure ($1R^*$,$2S^*$,$3S^*$,$5R^*$,$6S^*$)-2,3-dibromo-N-alkyl[3.2.0]heptan-6-amines (0.64 mmol) were dissolved in 25 ml of acetonitrile and only 0.64 (1 equiv.) of triethyl amine was added. The rest of the procedure is identical to that described above. This procedure is the preferred one because here the obtained compounds were perfectly pure.

8-(endo)Bromo-N-isopropyl-2-azatricyclo[3.3.0.0^{3,6}]octane 451a



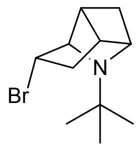
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.01 (3H, d, *J*= 6.3 Hz, CH_3), 1.22 (3H, d, *J*= 6.3 Hz, CH_3), 1.67 (1H, ddd, *J*= 8.3 Hz, *J*= 2 Hz, *J*= 2 Hz, $CH_{4a}\underline{H}_{4b}$), 1.80 (1H, dd, *J*= 13.2 Hz, *J*= 7.6 Hz, $C\underline{H}_{7a}H_{7b}$), 1.87 (1H, d, *J*= 8.3 Hz, $C\underline{H}_{4a}H_{4b}$), 1.95 (1H, ddd, *J*= 13.2 Hz, *J*= 9.6 Hz, *J*= 4.9 Hz, $CH_{7a}\underline{H}_{7b}$), 2.31-2.33 (1H, m, CH, 6), 2.54-2.64 (1H, m, CH, 5), 2.60 (1H, sept, *J*= 6.3 Hz, $NC\underline{H}(CH_3)_2$), 3.07 (1H, br. s, CH 1), 3.63 (1H, br. d, *J*= 6.6 Hz, CH 3), 4.10 (1H, ddd, *J*= 9.3 Hz, *J*= 7.5 Hz, *J*= 1.7 Hz, CHBr, 8). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 19.41 (CH_3), 23.38 (CH_3), 29.99 (CH_2, 4), 32.87 (CH_2, 7), 45.10 (CH, 5), 49.22 ($N\underline{C}H(CH_3)_2$), 51.36 (CH, 6), 54.02 (CHBr, 8), 63.79 (CH, 3), 67.89 (CH, 1). **IR (cm^{-1}) ν_{max} :** 2971. **MS: m/z (%):** (GC) 229/231 (M^+, 26), 216/214 (20), 150 (100), 108 (48), 91 (38), 80 (22). Yield = 81 %.

8-(endo)Bromo-N-propyl-2-azatricyclo[3.3.0.0^{3,6}]octane 451b



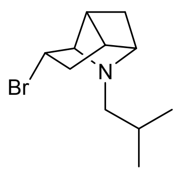
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 0.95 (3H, t, *J*= 7.4 Hz, $NCH_2CH_2C\underline{H}_3$), 1.59-1.7 (2H, m, $NCH_2C\underline{H}_2CH_3$), 1.65-1.75 (1H, m, $C\underline{H}_{4a}H_{4b}$), 1.84 (1H, dd, *J*= 13.4 Hz, *J*= 7.4 Hz, $C\underline{H}_{7a}H_{7b}$), 1.96 (1H, dd, *J*= 14.2 Hz, *J*= 8.6 Hz, $CH_{4a}\underline{H}_{4b}$), 1.98 (1H, dd, *J*= 13.4 Hz, *J*= 9.4 Hz, $CH_{7a}\underline{H}_{7b}$), 2.37-2.39 (1H, m, CH 6), 2.41-2.50 (2H, m, $NC\underline{H}_2CH_2CH_3$), 2.60-2.63 (1H, m, CH 5), 2.94 (1H, br. s, CH 1), 3.48 (1H, br. d, *J*= 6.6 Hz, CH 3), 4.10 (1H, ddd, *J*= 9.3 Hz, *J*= 7.5 Hz, *J*= 1.6 Hz, CHBr, 8). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 12.09 ($NCH_2CH_2\underline{C}H_3$), 22.35 ($NCH_2\underline{C}H_2CH_3$), 30.78 (CH$_2$, 4), 33.24 (CH$_2$, 7), 45.55 (CH, 5), 52.24 (CH, 6), 54.02 (CHBr, 8), 54.68 (NCH$_2$), 66.79 (CH, 3), 69.20 (CH, 1). **IR (cm^{-1}) ν$_{max}$:** 2934. **MS: m/z (%):** (GC) 231/229 (M$^+$, 20), 202/200 (16), 150 (100), 122 (17), 91 (21). Yield = 61 %.

8-(endo)Bromo-N-t-butyl-2-azatricyclo[3.3.0.0^{3,6}]octane 451c



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.16 (9H, s, t-Bu), 1.69 (1H, br. d, *J*= 8.3 Hz, $C\underline{H}_{4a}H_{4b}$), 1.74 (1H, dd, *J*= 12.6 Hz, *J*= 7.9 Hz, $C\underline{H}_{7a}H_{7b}$), 1.81 (1H, d, *J*= 7.9 Hz, $CH_{4a}\underline{H}_{4b}$), 1.87 (1H, ddd, *J*= 12.6 Hz, *J*= 8.9 Hz, *J*= 4.6 Hz, $CH_{7a}\underline{H}_{7b}$), 2.25-2.26 (1H, m, CH 6), 2.52-2.55 (1H, m, CH 5), 3.43 (1H, br. s, CH 1), 3.64 (1H, br. d, *J*= 6.6 Hz, CH 3), 4.06 (1H, dt, *J*= 8.5 Hz, *J*= 1 Hz, CHBr, 8). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 30.37 (CH$_3$, t-Bu), 32.90 (CH$_2$, 7), 34.54 (CH$_2$, 4), 44.92 (CH, 5), 52.27 (C$_{quat.}$, t-Bu), 52.58 (CH, 6), 54.91 (CHBr, 8), 63.61 (CH, 1), 64.08 (CH, 3). **IR (cm^{-1}) ν$_{max}$:** 2968. **MS: m/z (%):** (GC) 245/243 (M$^+$, 13), 230/228 (20), 164 (21), 108 (100), 91 (32), 80 (17). Yield = 72 %.

8-(endo)Bromo-N-isobutyl-2-azatricyclo[3.3.0.0^{3,6}]octane 451d



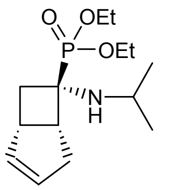
^{1}H-NMR (270 MHz, CDCl$_3$) δ: 0.95 (3H, d, *J*= 6.6 Hz, CH$_3$), 1.01 (3H, d, *J*= 6.6 Hz, CH$_3$), 1.67-1.98 (5H, m, CH$_2$ 4, CH$_2$ 7, $NCH_2C\underline{H}(CH_3)_2$), 2.16 (1H, dd, *J*= 12.2 Hz, *J*= 7.9 Hz, $NC\underline{H}_aH_b$), 2.36 (1H, dd, *J*= 12.3 Hz, *J*= 6.1 Hz, $NCH_a\underline{H}_b$), 2.33-2.35 (1H, m, CH 6), 2.56-2.60 (1H, m, CH 5), 2.85 (1H, br. s, CH 1), 3.37 (1H, d, *J*= 6.6 Hz, CH 3), 4.07 (1H, ddd, *J*= 9.2 Hz, *J*= 7.6 Hz, *J*= 1.3 Hz, CHBr, 8). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 21.11 (CH$_3$), 21.33 (CH$_3$), 27.76 ($NCH_2\underline{C}H(CH_3)_2$), 31.11 (CH$_2$, 4), 33.39 (CH$_2$, 7), 45.52 (CH, 5), 52.24 (CH, 6), 54.81 (CHBr, 8), 61.51 ($N\underline{C}H_2CH(CH_3)_2$), 70.60 (CH, 1). **IR (cm^{-1}) ν$_{max}$:** 2974 (br.). **MS: m/z (%):** (GC) 245/243 (M$^+$, 16), 202/200 (60), 164 (100), 120 (16), 108 (35). Yield = 84 %.

6.14.4. Entry to diethyl 8-(endo)bromo-2-azatricyclo[3.3.0.0^{3,6}]octan-3-yl phosphonate

Diethyl (1*S**,5*R**,6*R**)-[6-(isopropylamino)bicyclo[3.2.0]hept-2-en-6-yl]phosphonate 471

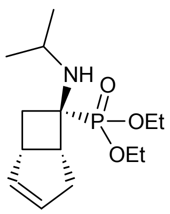
In a flask of 100 ml (under a N$_2$ atmosphere), 1.61 g triethyl amine (1.2 equiv., 16 mmol) and 2.04 g diethyl phosphite (1.1 equiv., 1.4 mmol) were stirred in 40 ml of dry dichloromethane for

30 minutes at 0°C. 1.75 g Trimethylsilyl chloride was added dropwise using a syringe. After stirring for another 30 minutes 1.96 g N-[bicyclo[3.2.0]hept-2-en-6-ylideen]-N-isopropyl amine (1.0 equiv., 13 mmol) was added dropwise. The reaction was completed after 13 days. The reaction mixture was extracted twice with 100 ml of a 2N HCl solution. The water layer was basified using a 4N NaOH solution and extracted with dichloromethane (3 x 70 ml). The combined organic phases were dried with $MgSO_4$ overnight. After filtration and evaporation of the solvent 2.20 g of product is obtained (32 mmol, 58 % yield) as a mixture of diastereoisomers (92/8 derived from ^{31}P-NMR). Separation of the isomers was performed using flash chromatography. The major compound (R_f= 0.39) was obtained as an oil with a yield of 55 %. The other isomer was isolated as an oil with a yield of 6 % (R_f= 0.19).



MAJOR: **^{1}H-NMR (270 MHz, CDCl$_3$) δ:** 1.03 (3H, d, *J*= 6.3 Hz, NCH(C$\underline{H}_3$)$_2$), 1.04 (3H, d, *J*= 6.3 Hz, NCH(C$\underline{H}_3$)$_2$), 1.35 (6H, dt, *J*= 7.0 Hz, *J*= 1.7 Hz, 2 x OCH$_2$C$\underline{H}_3$), 1.79 (1H, ddd, *J*= 17.9 Hz, *J*= 12.6 Hz, *J*= 5.2 Hz, C$\underline{H}_{7a}$H$_{7b}$), 2.40 (1H, ddd, *J*= 17.5 Hz, *J*= 9.4 Hz, *J*= 1.5 Hz, C$\underline{H}_{4a}$H$_{4b}$), 2.63-2.79 (1H, m, CH$_{7a}$$\underline{H}_{7b}$), 2.88 (1H, dddd, *J*= 17.5 Hz, *J*= 5.4 Hz, *J*= 2.7 Hz, *J*= 2.6 Hz, CH$_{4a}$$\underline{H}_{4b}$), 3.10-3.30 (3H, m, CH 1 + NC$\underline{H}$(CH$_3$)$_2$), 4.18 (2H, dq, *J*= 7.3 Hz, *J*= 1.0 Hz, OC$\underline{H}_2$CH$_3$), 4.21 (2H, dq, *J*= 7.3 Hz, *J*= 1.0 Hz, OC$\underline{H}_2$CH$_3$), 5.72-5.76 (1H, m, CH= 2), 5.80-5.82 (1H, m, CH= 3). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 16.63 (d, *J*= 6.1 Hz, OCH$_2$$\underline{C}H_3$), 24.78 (NHCH($\underline{C}H_3$)$_2$), 25.35 (NHCH($\underline{C}H_3$)$_2$), 32.51 (d, *J*= 4.9 Hz, CH$_2$ 4), 36.08 (CH$_2$ 7), 40.49 (d, *J*= 6.1 Hz, CH 1), 41.85 (d, *J*= 2.4 Hz, CH 5), 45.29 (d, *J*= 3.6 Hz, N$\underline{C}$H(CH$_3$)$_2$), 56.14 (d, *J*= 148.3 Hz, C$_{quat.}$), 62.02 (d, *J*= 8.0 Hz, O$\underline{C}$H$_2$CH$_3$), 62.07 (d, *J*= 8.0 Hz, O$\underline{C}$H$_2$CH$_3$), 132.54 (CH=, 3), 133.91 (CH=, 2). **IR (cm^{-1}) ν$_{max}$:** 3470 (NH), 1244 (P=O). **MS: m/z (%):** (direct inlet) 287 (M$^+$, 11), 244 (15), 221 (68), 206 (31), 178 (17), 177 (26), 150 (37), 138 (18), 111 (53), 108 (23), 107 (23), 106 (24), 84 (49), 83 (100), 65 (35). **Chromatography**: EtOAc/MeOH/Hex 96/2/2 R_f= 0.39. **^{31}P-NMR (109 MHz, CDCl$_3$) δ:** 29.86 ppm.

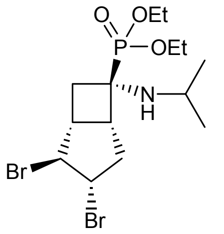
diethyl (1*S,5*R**,6*S**)-[6-(isopropylamino)bicyclo[3.2.0]hept-2-en-6-yl]phosphonate 472**



MINOR: **^{1}H-NMR (270 MHz, CDCl$_3$) δ:** 1.13 (6H, d, *J*= 6.3 Hz, NCH(C$\underline{H}_3$)$_2$), 1.30 (6H, dt, *J*= 7.1 Hz, *J*= 1.7 Hz, 2 x OCH$_2$C$\underline{H}_3$), 2.03-2.14 (1H, m, C$\underline{H}_{7a}$H$_{7b}$), 2.33 (1H, dt, *J*= 13.2 Hz, *J*= 5.0 Hz, CH$_{7a}$$\underline{H}_{7b}$), 2.55 (1H, dd, *J*= 17.7 Hz, *J*= 10.4 Hz, C$\underline{H}_{4a}$H$_{4b}$), 2.87-3.01 (1H, m, CH$_{4a}$$\underline{H}_{4b}$), 2.91-3.01 (1H, m, CH 5), 3.29 (1H, dh, *J*= 6.4 Hz, *J*= 1.2 Hz, NC$\underline{H}$(CH$_3$)$_2$), 3.35-3.48 (1H, m, CH 1), 4.04-4.16 (4H, m, 2 x OC$\underline{H}_2$CH$_3$), 5.68-5.71 (1H, m, CH=), 5.76-5.79 (1H, m, CH=). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 16.58 (d, *J*= 6.2 Hz, 2 x OCH$_2$$\underline{C}H_3$), 25.03 (NHCH($\underline{C}H_3$)$_2$), 25.39 (NHCH($\underline{C}H_3$)$_2$), 35.81 (d, *J*= 2.5 Hz, CH$_2$ 4), 38.27 (CH$_2$ 7), 40.75 (d, *J*= 10.9 Hz, CH 1), 45.05 (d, *J*= 4.8 Hz, CH 5), 45.97 (d, *J*= 3.7 Hz, NH$\underline{C}$H(CH$_3$)$_2$), 60.42 (d, *J*= 138.0 Hz, C$_{quat.}$), 61.08 (d, *J*= 7.3 Hz, O$\underline{C}$H$_2$CH$_3$), 61.75 (d, *J*= 8.5 Hz, O$\underline{C}$H$_2$CH$_3$), 132.16 ($\underline{C}$H=$\underline{C}$H). **IR (cm^{-1}) ν$_{max}$:** 3437 (NH), 1234 (P=O). **MS: m/z (%):** (ES, Pos) 150 (100). **Chromatography**: EtOAc/MeOH/Hex 96/2/2 R_f= 0.19. **^{31}P-NMR (109 MHz, CDCl$_3$) δ:** 26.19 ppm.

Diethyl (1*R,2*S**,3*S**,5*R**,6*R**)-2,3-dibromo-6-(isopropylamino)bicyclo[3.2.0]hept-6-yl phosphonate 473**

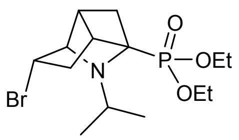
This compound was prepared in the same way to prepare the 2,3-dibromo-N-alkyl[3.2.0]heptan-6-amines. The product was isolated as an oil.



^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.05 (3H, d, *J*= 6.3 Hz, $NCH(C\underline{H}_3)_2$), 1.08 (3H, d, *J*= 6.0 Hz, $NCH(C\underline{H}_3)_2$), 1.36 (6H, t, *J*= 7.1 Hz, 2 x $OCH_2C\underline{H}_3$), 2.33 (1H, ddd, *J*= 20.2 Hz, *J*= 12.9 Hz, *J*= 7.5 Hz, $C\underline{H}_{7a}H_{7b}$), 2.50-2.62 (1H, ddd, *J*= 15.3 Hz, *J*= 9.1 Hz, *J*= 7.3 Hz, $C\underline{H}_{4a}H_{4b}$), 2.70-2.87 (2H, m, $CH_{4a}\underline{H}_{4b}$ + $CH_{7a}\underline{H}_{7b}$), 3.02-3.12 (1H, m, CH 1), 3.19-3.34 (2H, m, $NC\underline{H}(CH_3)_2$ + CH 5), 4.19 (2H, dq, *J*= 7.5 Hz, *J*= 1.7 Hz, $OC\underline{H}_2CH_3$), 4.21 (2H, dq, *J*= 7.0 Hz, *J*= 1.7 Hz, $OC\underline{H}_2CH_3$), 4.34 (1H, dd, *J*= 4.9 Hz, *J*= 2.5 Hz, CHBr 2), 4.47 (1H, ddd, *J*= 4.9 Hz, *J*= 6.6 Hz, *J*= 6.7 Hz, CHBr 3). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 16.59 (d, *J*= 6.1 Hz, 2 x $OCH_2\underline{C}H_3$), 24.13 ($NCH(\underline{C}H_3)_2$), 24.65 ($NCH(\underline{C}H_3)_2$), 34.58 (d, *J*= 6.1 Hz, CH_2 4), 36.33 (CH_2 7), 43.93 (d, *J*= 2.4 Hz, CH 1), 45.38 (d, *J*= 3.6 Hz, CH 5), 46.07 ($N\underline{C}H(CH_3)_2$), 53.93 (d, *J*= 150.1 Hz, $C_{quat.}$), 56.46 (CHBr 3), 60.50 (CHBr 2), 62.25 (d, *J*= 8.5 Hz, $O\underline{C}H_2CH_3$), 62.38 (d, *J*= 8.5 Hz, $O\underline{C}H_2CH_3$). **IR (cm^{-1}) ν_{max} :** 3311 (NH), 1247 (P=O). **Chromatography**: 100% EtOAc R_f= 0.30. **^{31}P-NMR (109 MHz, CDCl$_3$) δ:** 28.98 ppm.

Diethyl 8-(endo)bromo-2-azatricyclo[3.3.0.0^{3,6}]octan-3-yl phosphonate 474

This compound was prepared in the same way the 8-(endo)bromo-N-alkyl-2-azatricyclo[3.3.0.0^{3,6}]octanes were prepared. The product was isolated as an liquid oil.

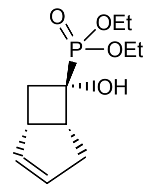


^{1}H-NMR (270 MHz, CDCl$_3$) δ: 1.07 (3H, d, *J*= 6.6 Hz, $NCH(C\underline{H}_3)_2$), 1.30 (3H, d, *J*= 6.6 Hz, $NCH(C\underline{H}_3)_2$), 1.34 (3H, t, *J*= 7.1 Hz, $OCH_2C\underline{H}_3$), 1.36 (3H, t, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 1.88 (1H, dd, *J*= 13.5 Hz, *J*= 8.1 Hz, $C\underline{H}_{7a}H_{7b}$), 1.91-2.01 (1H, m, $CH_{7a}\underline{H}_{7b}$), 2.06 (1H, d, *J*= 8.2 Hz, $C\underline{H}_{4a}H_{4b}$), 2.14 (1H, dd, *J*= 8.2 Hz, *J*= 1.0 Hz, $CH_{4a}\underline{H}_{4b}$), 2.61 (1H, d, *J*= 4.0 Hz, CH 6), 2.66 (1H, d, *J*= 22.1 Hz, CH 5), 3.50 (1H, sept., *J*= 6.6 Hz, $NC\underline{H}(CH_3)_2$), 3.55 (1H, br. s, NCH 1), 4.04-4.18 (1H, m, CHBr), 4.06-4.30 (4H, m, $OC\underline{H}_2CH_3$). **^{13}C-NMR (68 MHz, CDCl$_3$) δ:** 16.52 (d, *J*= 7.3 Hz, $OCH_2\underline{C}H_3$), 21.92 ($NCH(\underline{C}H_3)_2$), 26.34 ($NCH(\underline{C}H_3)_2$), 32.60 (CH_2 7), 35.69 (d, *J*= 7.3 Hz, CH_2 4), 44.68 (d, *J*= 25.6 Hz, CH 5), 49.45 ($N\underline{C}H(CH_3)_2$), 53.85 (CHBr), 55.94 (CH 6), 61.37 (d, *J*= 6.1 Hz, $O\underline{C}H_2CH_3$), 62.33 (d, *J*= 6.1 Hz, $O\underline{C}H_2CH_3$), 65.32 (d, *J*= 14.7 Hz, NCH 1), 71.36 (d, *J*= 175.8 Hz, $C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 1243 (P=O). **MS: m/z (%):** (direct inlet) 365/367 (M^+, 1), 286 (43), 216 (27), 188 (34), 148 (24), 106 (100), 79 (21). **^{31}P-NMR (109 MHz, CDCl$_3$) δ:** 20.77 ppm. Yield = 92 %.

6.15. Entry to the 2-oxatricyclo[3.2.1.0^{3,6}]octane or 2-oxatricyclo[3.3.0.0^{3,6}]octane skeleton

Diethyl (1*S,5*R**,6*R**)-6-hydroxybicyclo[3.2.0]hept-2-en-6-yl phosphonate 475**

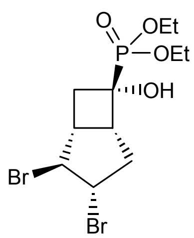
To a flask containing 4.3 g (1.1 equiv.) diethyl phosphite, 3 g of bicyclo[3.2.0]hept-2-en-6-one was added without solvent and the mixture was heated at 60°C for an overnight period (a cooler and $CaCl_2$-tube were present). The resulting solution contains the diethyl 6-hydroxybicyclo[3.2.0]hept-2-en-6-yl phosphonate and some amount of diethyl phosphite which was removed by column chromatography (short column). 4.08 g of pure diethyl (1*S**,5*R**,6*R**)-6-hydroxybicyclo[3.2.0]hept-2-en-6-yl phosphonate was obtained which crystallises at -18°C but melts at room temperature (yield = 60 %).



^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.34 (6H, dt, *J*= 7.1 Hz, *J*= 1.3 Hz, $OCH_2C\underline{H}_3$), 1.78 (1H, tdd, *J*= 12.5 Hz, *J*= 4.7 Hz, *J*= 1 Hz, $C\underline{H}_aH_b$ 7), 2.42 (1H, ddd, *J*= 17.1 Hz, *J*= 9.8 Hz, *J*= 0.9 Hz, $C\underline{H}_aH_b$ 4), 2.78-2.92 (2H, m, $CH_a\underline{H}_b$ 4 + $CH_a\underline{H}_b$ 7), 3.06-3.11 (1H, m, CH 1), 3.26-3.37 (1H, m, CH 5), 3.98 (1H, br. s, OH), 4.11-4.22 (4H, m, $OC\underline{H}_2CH_3$), 5.77-5.86 (2H, m, $C\underline{H}=C\underline{H}$). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 15.89 (d, *J*= 4.9 Hz, $OCH_2\underline{C}H_3$), 31.05 (d, *J*= 4.9 Hz, CH_2 4), 38.13 (s, CH_2 7), 39.00 (d, *J*= 9.8 Hz, CH 1), 41.06 (s, CH, 5), 61.94 (d, *J*= 7.3 Hz, $O\underline{C}H_2CH_3$), 62.00 (d, *J*= 7.3 Hz, $O\underline{C}H_2CH_3$), 69.48 (d, *J*= 162 Hz, $C_{quat.}$), 132.09 (s, $\underline{C}H=CH$), 133.48 (s, $CH=\underline{C}H$). **IR (cm^{-1}) ν_{max} :** 3271 (br., OH), 1293. **MS: m/z (%):** (GC) 246 (M^+, 11), 181 (100), 153 (33), 138 (46), 125 (68), 111 (48), 66 (92). **Chromatography**: 98/2 EtOAc/MeOH R_f= 0.26. **^{31}P-NMR (109 MHz, $CDCl_3$) δ:** 24.93 ppm.

Diethyl (1*R,2*S**,3*S**,5*R**,6*R**)-2,3-dibromo-6-hydroxybicyclo[3.2.0]hept-6-yl phosphonate 476**

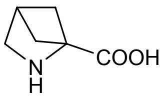
The diethyl (1*S**,5*R**,6*R**)-6-hydroxybicyclo[3.2.0]hept-2-en-6-yl phosphonate was brominated in the same way as the N-alkylbicyclo[3.2.0]hept-2-en-6-amines with the exception that hydrobromic acid was not used (yield = 89 %). The product was isolated as a white powder.



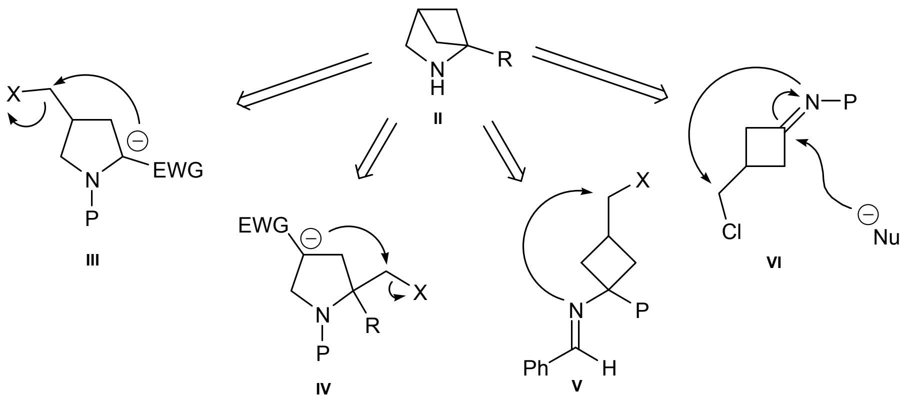
^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.34 (6H, dt, *J*= 7.0 Hz, *J*= 2.0 Hz, $OCH_2C\underline{H}_3$), 2.40-2.90 (5H, m, CH_2 4 + CH_2 7 + CH 1), 3.28-3.33 (1H, m, CH 5), 4.12-4.24 (4H, m, $OC\underline{H}_2CH_3$), 4.41-4.43 (1H, m, $C\underline{H}BrCH$), 4.47-4.53 (1H, m, $CHBrCH_2$), 5.42 (1H, d, *J*= 5.0 Hz, OH). **^{13}C-NMR (68 MHz, $CDCl_3$) δ:** 16.51 (d, *J*= 4.9 Hz, $OCH_2\underline{C}H_3$), 33.24 (d, *J*= 4.8 Hz, CH_2 4), 37.30 (s, CH_2 7), 42.49 (d, *J*= 6.1 Hz, CH 1), 45.26 (d, *J*= 2.5 Hz, CH 5), 56.06 ($\underline{C}HBrCH_2$), 60.66 (d, *J*= 3.6 Hz, $\underline{C}HBrCH$), 63.0 (d, *J*= 7.3 Hz, $O\underline{C}H_2CH_3$), 67.05 (d, *J*= 167.3 Hz, $C_{quat.}$). **IR (cm^{-1}) ν_{max} :** 3247 (br., OH), 1233. **MS: m/z (%):** (direct inlet) 408/406/404 (33), 245 (19), 180 (43), 138 (100), 111 (45). **Chromatography**: 98/2 EtOAc/MeOH R_f= 0.32. **^{31}P-NMR (109 MHz, $CDCl_3$) δ:** 24.47 ppm. **Mp.**: 87.6-88.7°C.

7. Summary

One of the frequently used defence mechanisms of plants against predators is the accumulation of high quantities of non-protein amino acids in the seeds. 2,4-Methanoproline **I** is an amino acid isolated from the seeds of *Ateleia Herbert-smithii Pittier*. The seeds of this tree are neglected by more than 100 different seed predators, among which numerous insects and rodents. It is since the isolation and characterisation of 2,4-methanoproline that some authors attribute anti-feedant properties to this amino acid. However, no real screening of the biological activity of 2,4-methanoproline has been performed. Further, 2,4-methanoproline **I** does not behave like classical amino acids. Energy studies on proteins which contain 2,4-methanoproline indicate that this amino acid selectively stabilises the *trans* peptide bond. Therefore, the aim of this dissertation was to develop new entries to 2,4-methanoproline and its analogues **II**. Four different strategies were evaluated.

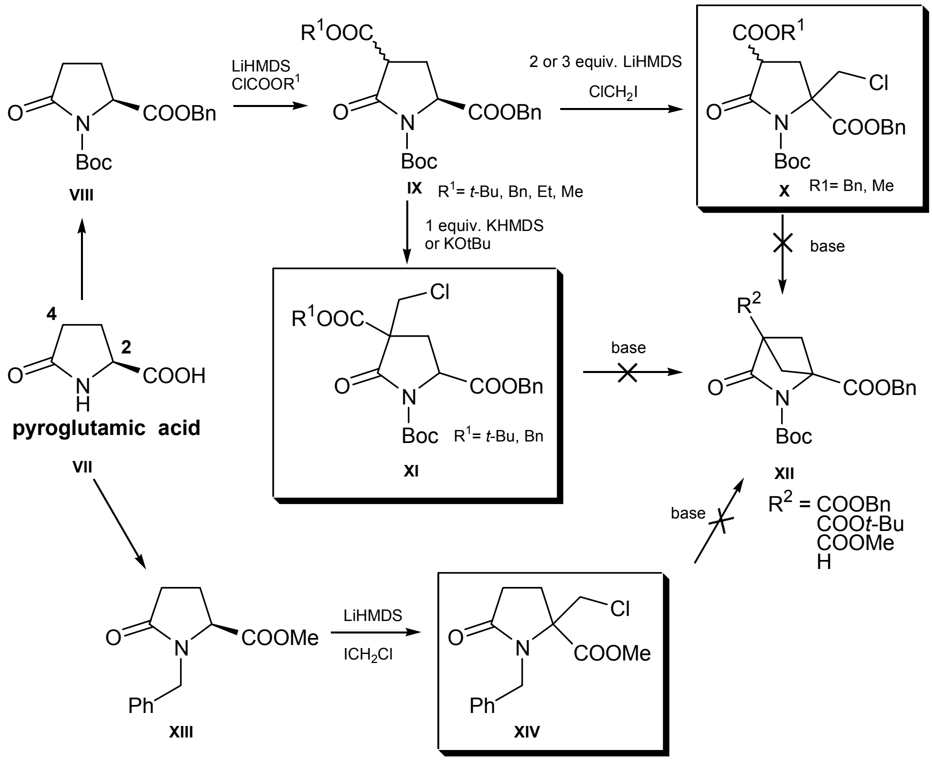


I
2,4-methanoproline

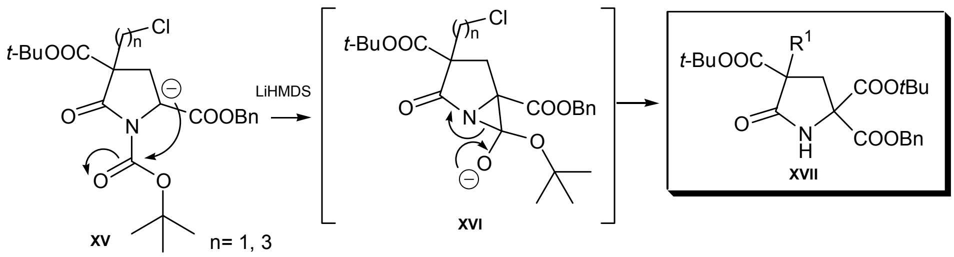


In the first two entries a suitable (chloromethyl)pyrrolidine **III**, **IV** were prepared to evaluate the formation of a 4-membered ring in an existing 5-membered ring. Such a pyrrolidine **III**, **IV** was constructed from pyroglutamic acid **VII**, by means of a Kharasch reaction or from an alkyl 4-methylene-2-pyrrolidinecarboxylate.

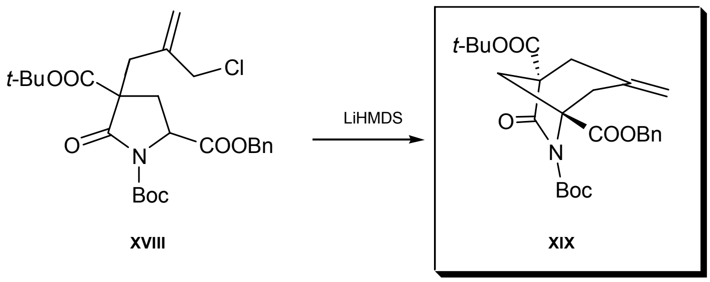
The protected pyroglutamate **VIII** could be alkylated at the 4-position. Direct alkylation of this compound using chloroiodomethane as electrophile was unsuccessful, therefore an alkoxycarbonyl group was first introduced at the 4-position. These compounds **IX** can be alkylated at the 4-position, using a potassium base such as KHMDS or KOtBu. Several derivatives were prepared and a chloromethyl group could be introduced at this position (**XI**). On the other hand, using 2 or 3 equivalents of LiHMDS, led to a change in regioselectivity and the electrophiles were introduced at the 2-position (e.g. **X**). By changing the N-protecting group from N-Boc **VIII** to N-Bn **XIII** alkylation could selectively be performed at the 2-position.



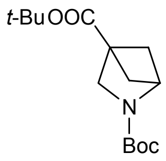
Attempts to deprotonate compounds **X**, **XI**, **XIV** either at the 2- or the 4-position with subsequent ring closure were not successful. Selective reduction of the amide bond of **XI** led to reaction mixtures. An interesting reaction took place when compounds **XV** were subjected to a treatment with base. No ring closure was observed (n = 1, 3) but instead the N-Boc group migrated to the 2-position (**XVII**). Other examples were performed illustrating the generality of this reaction.



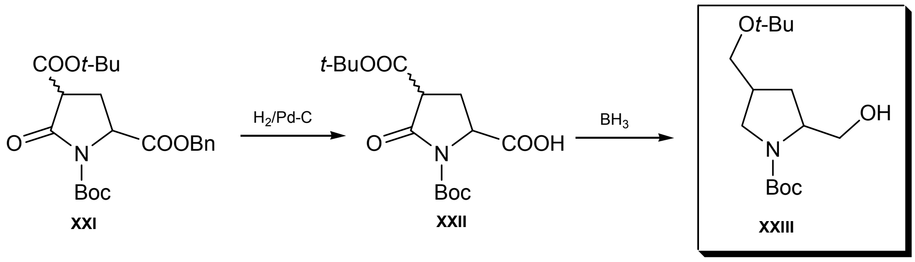
On the other hand, if the introduced group at the 4-position was a very good electrophile and the second formed ring was sufficiently large (6-membered ring in **XVIII**), ring closure occurred to the bicyclic compound **XIX**.



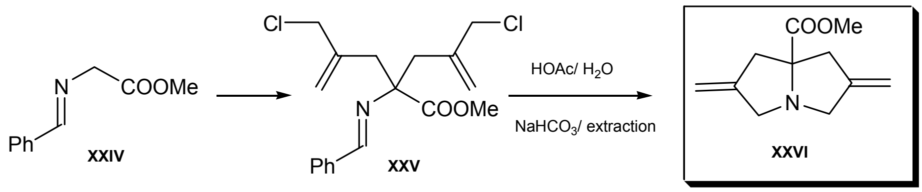
Another sequence was evaluated to prepare 2-azabicyclo[2.1.1]hexanes starting from the pyroglutamate **XXI**. The idea was to deprotect the benzyl ester, selectively reduce it to the corresponding alcohol and convert it to a suitable leaving group. Deprotonating adjacent to the remaining t-butyl ester could lead to the desired skeleton **XX**. Unfortunately reducing **XXII** with borane gave the t-butyl ether **XXIII**. This was very strange since the ester was not reduced to the alcohol but to the t-butyl ether.



XX

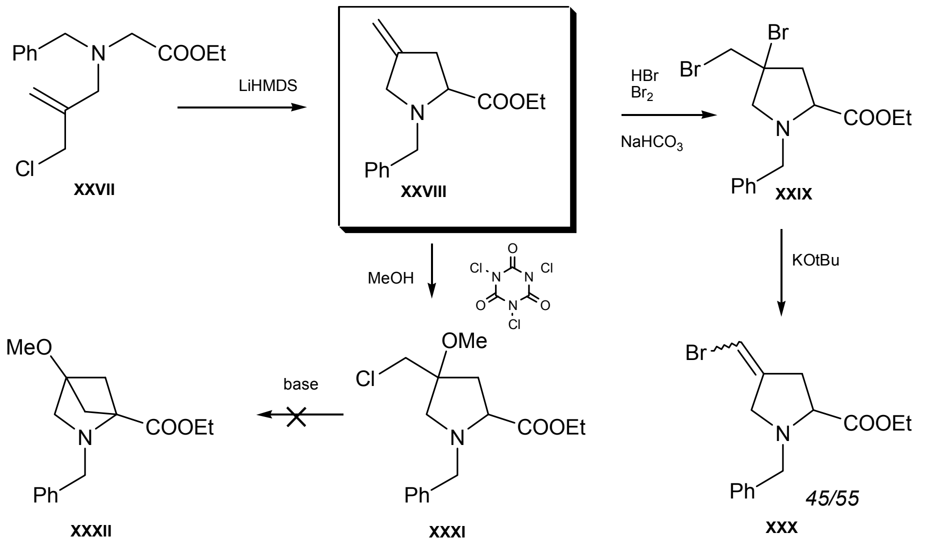


Other reaction schemes were evaluated to prepare alkyl 4-methylene-2-pyrrolidinecarboxylates. Attempts were made to mono alkylate, the imine **XXIV**, derived from glycine, using 3-chloro-2-(chloromethyl)-1-propene as electrophile. In all cases the dialkylated imine **XXV** was formed. After hydrolysis of the imine and basic workup, the pyrrolizine **XXVI**, could be isolated in good yield.

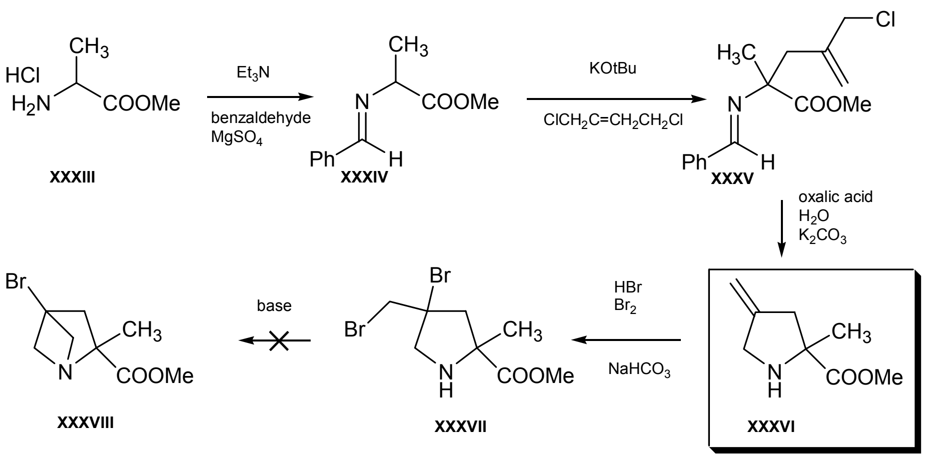


To avoid this double alkylation, ethyl N-benzyl glycinate was reacted with 3-chloro-2-(chloromethyl)-1-propene with formation of **XXVII**. Some dimer was formed which was removed by flash chromatography. By a good choice of reaction conditions, deprotonation of **XXVII** led to the 4-methylene-2-pyrrolidinecarboxylate **XXVIII** in an almost quantitative yield. Electophilic addition of bromine or methyl hypochlorite led to the production of **XXIX** and **XXXI** respectively.

Several attempts were tried for the ring closure of these compounds but despite the effort no bicyclic structure could be isolated.

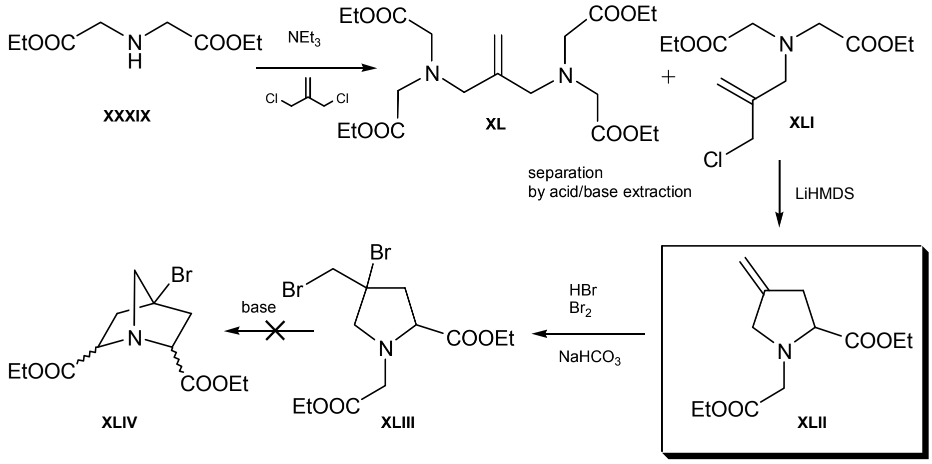


An entry to 1-azabicyclo[2.1.1]hexane **XXXVIII** was evaluated starting from methyl 2-aminopropanoate **XXXIII**. The imine **XXXIV** was alkylated with 3-chloro-2-(chloromethyl)-1-propene. After hydrolysing the imine **XXXV**, the pyrrolidine **XXXVI** was obtained. Bromination of the double bond led to **XXXVII** which was treated with a number of bases to construct the bicyclic compound **XXXVIII**. Unfortunately no suitable reaction conditions could be found leading to this product.



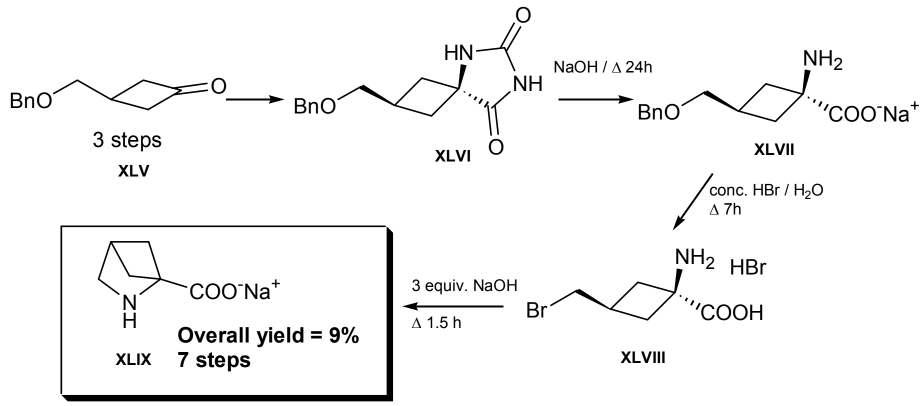
In the next pathway the aim was to construct the 1-azabicyclo[2.2.1]heptane skeleton starting from **XXXIX**. Reaction with 3-chloro-2-(chloromethyl)-1-propene led to a mixture of mono- **XLI** and di-alkylated product **XL** which could very easily be separated by acid/base extraction.

Treating **XLI** with a base gave the desired 4-methylene-pyrrolidine **XLII**. Deprotonating the brominated product **XLIII** with base did not lead to the desired 1-azabicyclo[2.2.1]heptane.

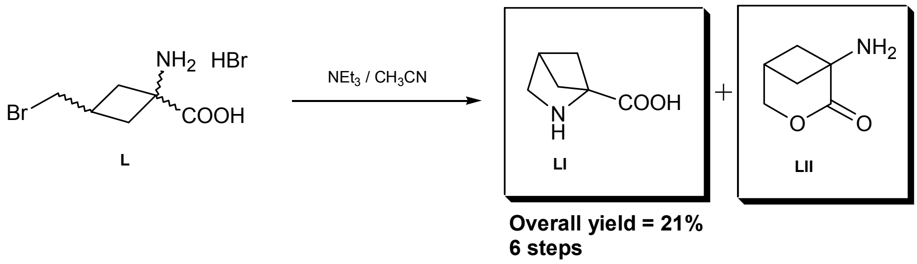


Since the construction of the 4-membered ring in an existing 5-membered ring was not successful, a different strategy was developed. In the following schemes, the 2-azabicyclo[2.1.1]hexane skeleton is formed by first constructing the 4-membered ring and subsequently ring closing these compounds to the bicyclic skeleton.

The natural 2,4-methanoproline could be prepared in 7 steps from allylbenzyl ether. Performing a [2+2]cycloaddition reaction and removing the geminal chloride atoms yielded the cyclobutanone **XLV**. The ketone function was transformed to the hydantoin (3/1 *cis/trans*) which was hydrolysed to the corresponding amino acid **XLVII**. To obtain the 2,4-methanoproline in pure form, a separation of the *cis*-hydantoin was performed (crystallisation, low yield). The ether group of **XLVII** was hydrolysed and converted to a bromomethyl group by heating this amino acid **XLVII** in a concentrated hydrobromic acid solution. Making the reaction alkaline led to the formation of 2,4-methanoproline (Na-salt, 7 steps, 9 % overall yield).

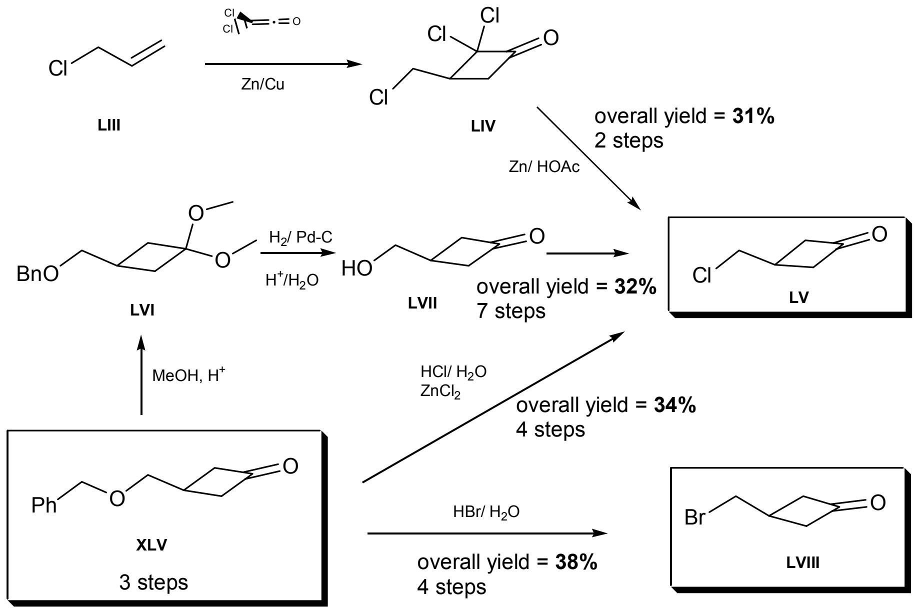


Because the separation of the hydantoin **XLVI** proved to be very difficult, the separation was performed in the last step. Heating the amino acid **L** (3/1 *cis/trans*) in acetonitrile gave the natural 2,4-methanoproline as a salt which was filtered off. Evaporating the filtrate gave the lactone **LII** which was formed out of the *cis*-isomer. The yield of 2,4-methanoproline was significantly improved since no separation of the hydantoin **XLVI** was necessary (6 steps, 21 % overall yield).



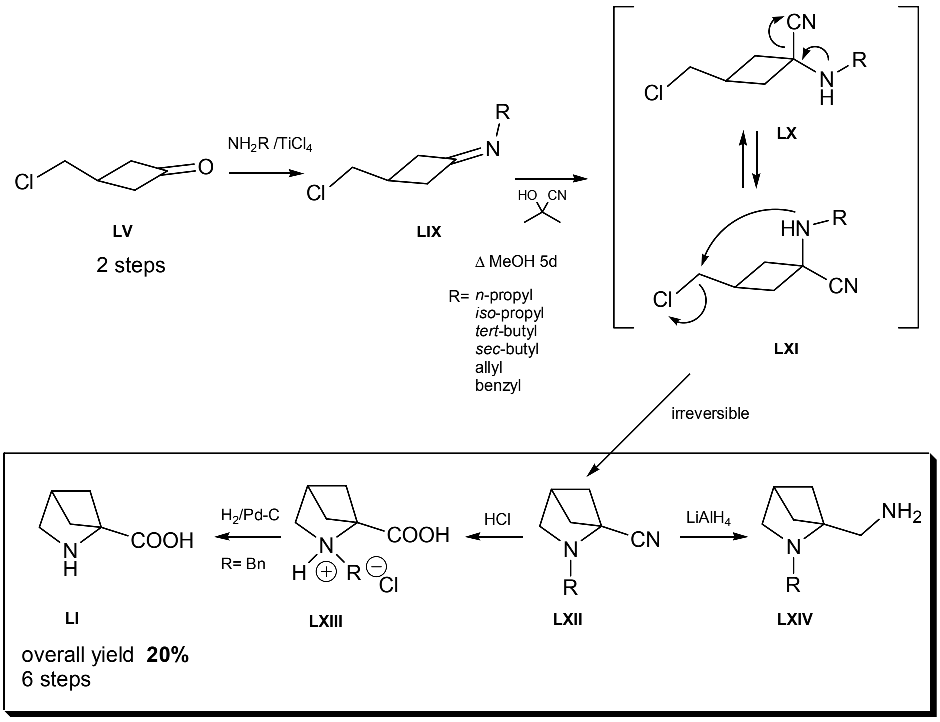
The cyclobutanone chemistry was rewarding and therefore reaction schemes starting from 3-(chloromethyl) cyclobutanone **LV** were developed. Only one preparation of this cyclobutanone was reported in the literature which was inconvenient for the synthesis on multi-gram scale. Therefore, new entries to this compound were developed.

In the first and most straightforward one, allyl chloride reacted with dichloroketene. Removing the geminal halogens, yielded the 3-(chloromethyl)cyclobutanone **LV** in 2 steps (31% overall yield).

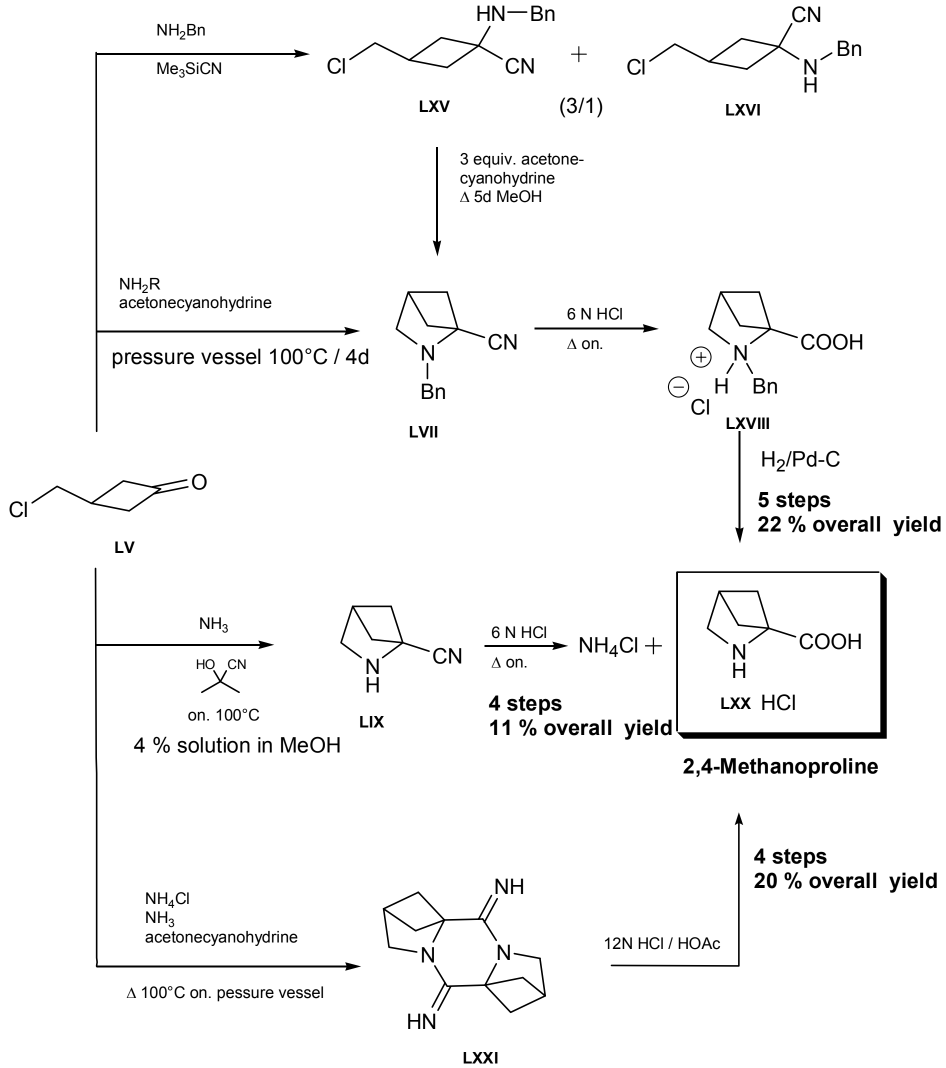


In a second pathway the cyclobutanone **XLV**, which can prepared on large scale, was converted to 3-(chloromethyl)cyclobutanone **LV** using different synthetic steps and shortcuts (7 steps, overall yield = 32 %).
This pathway could be shortened by performing the deprotection of the ether **XLV** and the conversion of the obtained alcohol to a good leaving group in the same step. This shortened the reaction sequence considerably (4 steps, overall yield 34%). The 3-bromomethyl cyclobutanone **LVIII** could be prepared using concentrated HBr instead of HCl (4 steps, 38 % overall yield).

The 3-(chloromethyl) cyclobutanone **LV** was converted to the imine **VIX**. These imines are very unstable in basic conditions. Reaction conditions were found allowing isomerisation between the amino nitriles **LX** and **LXI** and allowing ring closure of the amino nitrile **LXI**. Using this sequence the imines **LIX** were converted (without the formation of side products) in one step to the bicyclic amino nitriles **LXII**. The nitrile function could be hydrolysed to the amino acids **LXIII**. The natural 2,4-methanoproline **LI** was synthesised by deprotecting the N-benzyl group of **LXIII** (R= Bn) (6 steps, overall 20 %). The diamines **LXIV** were obtained after reduction of the cyanogroup with $LiAlH_4$.

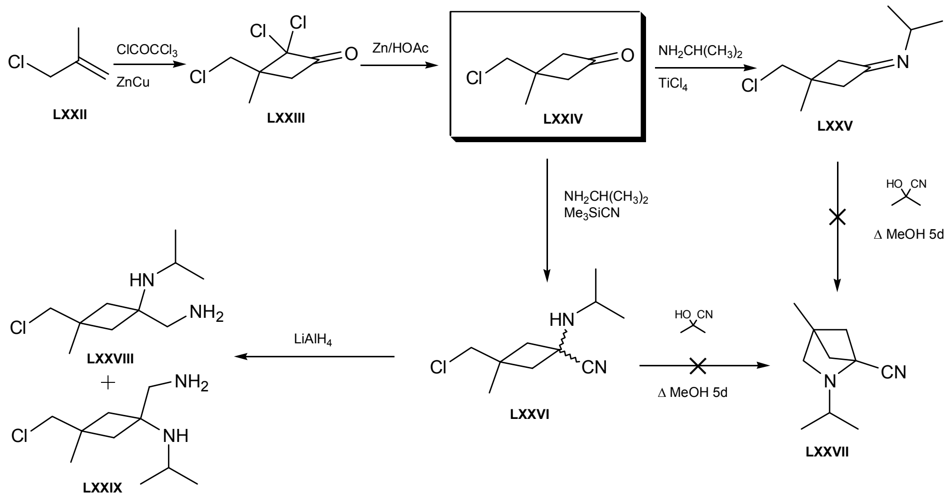


In the previous scheme 2,4-methanoproline was prepared in 6 steps. In the following overview several pathways and shortcuts to prepare 2,4-methanoproline are given.

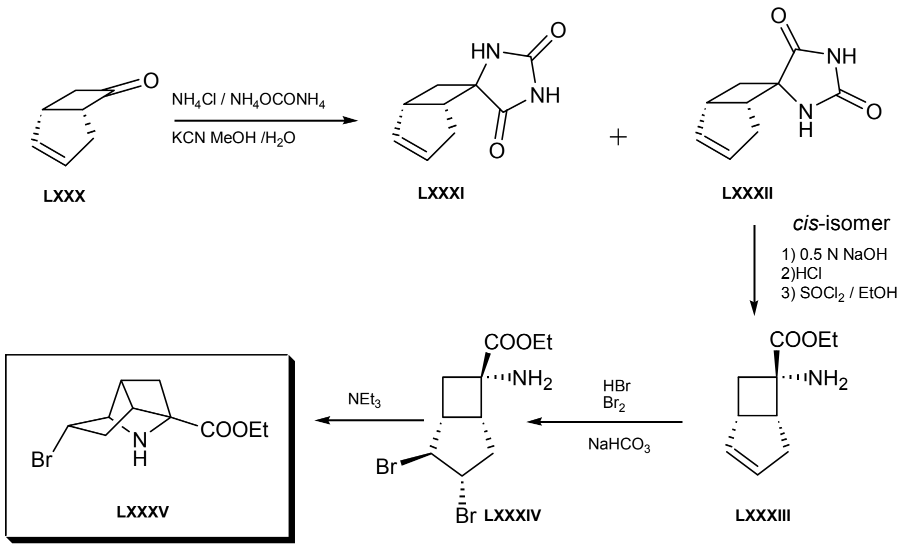


By changing the N-source and the reaction conditions the natural 2,4-methanoproline can now be synthesised in only 4 to 5 steps with an overall yield of approximately 20 %.

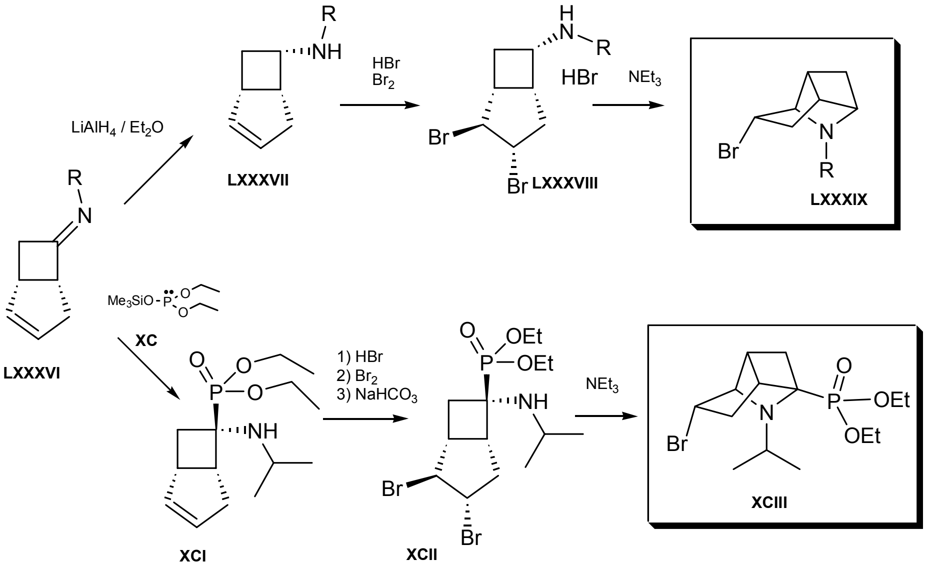
To prepare 2-azabicyclo[2.1.1]hexanes with substitution on the two bridgehead carbon atoms, the cyclobutanone **LXXIV** was prepared from methallyl chloride **LXXII**. Using the ideal reaction conditions for ring closure were unsuccessful and no bicyclic compound **LXXVII** could be isolated. Therefore, the amino nitrile **LXXVI** was prepared first and reduced to the corresponding amine. In this case, side products were formed and after purification only the amines **LXXVIII** and **LXXIX** were isolated. No ring closure of these compounds was observed.



The bicyclic ketone **LXXX** was used as starting material for the preparation of the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton. After converting the keto function to the hydantoin (3/1 *cis/trans*), hydrolysis and esterification gave the amino ester **LXXXIII**. The tricyclic skeleton was formed by brominating the double bond and heating this compound in basic medium. The very constrained tricyclic amino ester **LXXXV** was formed, consisting of the previously undescribed 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton.



An analogous sequence allowed the preparation of the tricyclic amines **LXXXIX**. The imine **LXXXVI** was reduced to the corresponding amines **LXXXVII** and **LXXXVII** which were separated by column chromatography. After bromination and ring closure, the desired tricyclic amines **LXXXIX** were isolated.



The methodology not only allowed the synthesis of tricyclic amines or amino esters but applies also to the synthesis of tricyclic amino phosphonates. The diastereomeric amino phosphonates, obtained after the addition of phosphite **XC** on the imine **LXXXVI**, were separated and converted through an analogous pathway to the tricyclic amino phosphonate **XCIII**.

In conclusion, several entries to the 2-azabicyclo[2.1.1]hexane skeleton were evaluated. All pathways where the synthesis of the bicyclic skeleton was evaluated by formation of a 4-membered ring in an existing 5-membered ring failed. On the other hand the preparation of 2,4-methanoproline and its analogues containing the 2-azabicyclo[2.1.1]hexane skeleton starting from a suitable cyclobutanone were very successful. New pathways were constructed to 3-halomethyl cyclobutanones which are the ideal starting materials to prepare this bicyclic skeleton.

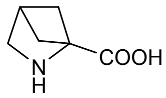
The methodology was expanded for the synthesis of tricyclic compounds. A very convenient entry to 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton was developed. Tricyclic amines, amino phosphonates and an amino ester were prepared.

Methanoproline and analogues were screened for their potential anti-feedant activity. The natural 2,4-methanoproline showed no activity on the larvae tested. On the other hand some of the derivatives show a significant anti-feedant property.

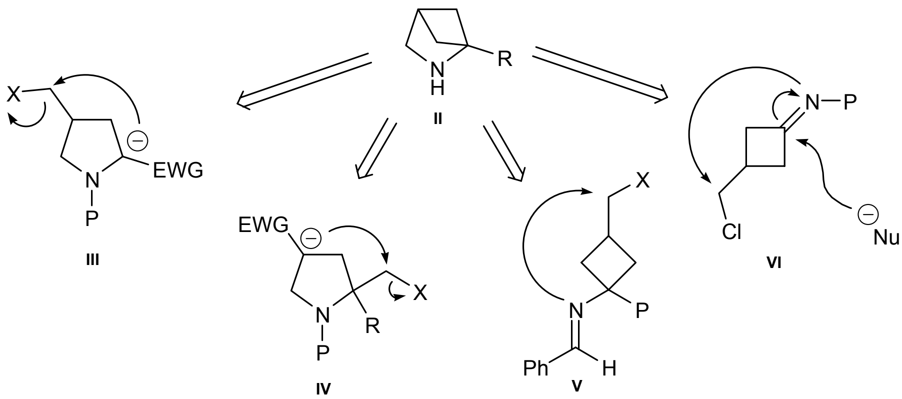
Some areas need further investigation, such as the one step conversion of 3-(chloromethyl) cyclobutanone to the 2-azabicyclo[2.1.1]hexane-1-carbonitrile and the asymmetric synthesis of the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton which might be useful as a chiral auxiliary.

8. Samenvatting

Een veel voorkomend afweersysteem van hogere planten tegen predatoren is het opslaan van grote hoeveelheden niet-proteogene aminozuren in de zaden. 2,4-Methanoproline **I** is een dergelijk natuurlijk aminozuur geïsoleerd uit *Ateleia Herbert-smithii Pittier*. De zaden van deze boom worden genegeerd door meer dan 100 zaadpredatoren, waaronder talrijke insecten en knaagdieren. Sinds de isolatie en karakterisatie van 2,4-methanoproline wordt door sommige auteurs een anti-feedant activiteit aan dit aminozuur toegeschreven. Tot op heden werd er echter nog geen uitgebreide screening uitgevoerd wegens de beperkte toegankelijkheid van deze verbinding. Naast de vermoedelijke anti-feedant werking bezit 2,4-methanoproline nog andere merkwaardige eigenschappen. Indien dit aminozuur wordt ingebouwd in een eiwit, zal het selectief de *trans* peptidenbinding vormen. Een dergelijk proline-analoog kan interessant zijn bij het onderzoek naar *cis/trans* isomerisatie in peptiden. Om deze redenen werden in dit doctoraat nieuwe toetredingen tot 2,4-methanoproline en analoga ontwikkeld. Het onderstaande schema geeft de retrosynthetische aanpak weer.

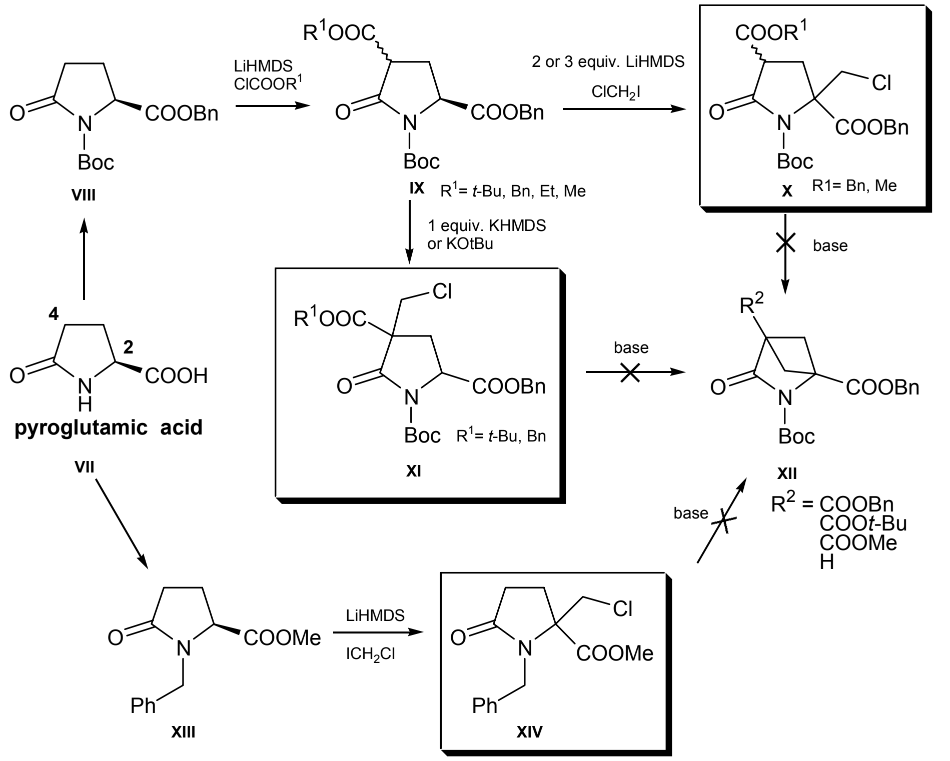


I
2,4-methanoproline

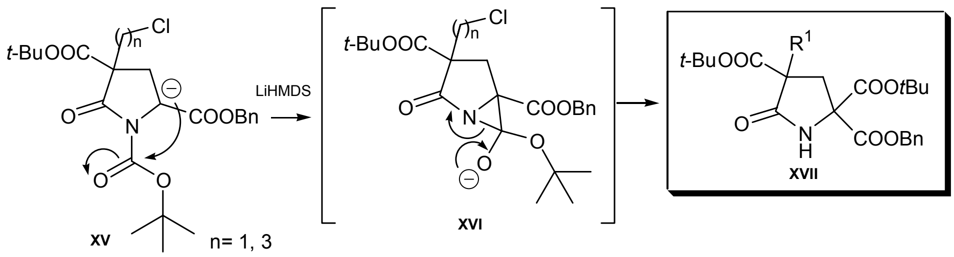


In de twee eerste toetredingen werden geschikte (chloormethyl)pyrrolidines **III** en **IV** bereid. Er werd onderzocht hoe een 4-ring kan gevormd worden in een bestaande 5-ring. Dergelijke pyrrolidines **III**, **IV** werden gesynthetiseerd uitgaande van L-pyroglutaminezuur of een alkyl 4-methyleen-2-pyrrolidinecarboxylaat.

Het beschermde pyroglutamaat **VIII** kon gealkyleerd worden op de 4-positie. De directe invoering van een chloormethyl groep bleek onmogelijk, daarom werd voorafgaandelijk een alkoxycarbonyl groep ingevoerd. Dergelijke verbindingen **IX** kunnen eenvoudig gealkyleerd worden in de 4-positie gebruik makend van een kalium base zoals KHMDS of KOtBu. Verschillende derivaten werden gesynthetiseerd en een chloormethyl groep werd ingevoerd op deze positie (**XI**). Door 2 of 3 equivalenten LiHMDS te gebruiken werd een verandering in regioselectiviteit waargenomen. Hierdoor werden elektrofielen geïntroduceerd in de 2-positie (bv. **X**). Een andere mogelijkheid om de 2-positie te derivatiseren is het wijzigen van de N-beschermende groep van N-Boc **VIII** naar N-benzyl **XIII**.



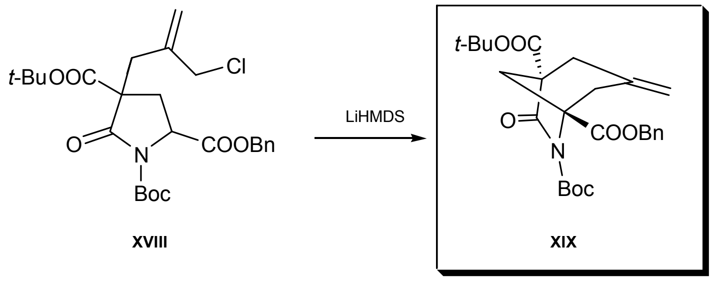
De ringsluiting van de verbindingen **X**, **XI**, **XIV** werd geëvalueerd door enerzijds de 2- en anderzijds de 4-positie te deprotoneren. In geen van deze gevallen bleek het echter mogelijk bicyclische verbindingen te bereiden. Een selectieve reductie van de amide functie om de structuur meer flexibel te maken bleek onmogelijk. Er werd echter een zeer interessante reactie waargenomen wanneer **XV** gedeprotoneerd werd met LiHMDS (base).



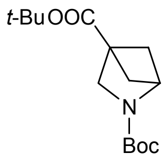
Ringsluiting (n = 1, 3) vond niet plaats maar de Boc-groep migreerde van N naar de 2-positie

(**XVII**). Dat deze reactie kan worden veralgemeend werd bewezen aan de hand van verschillende voorbeelden.

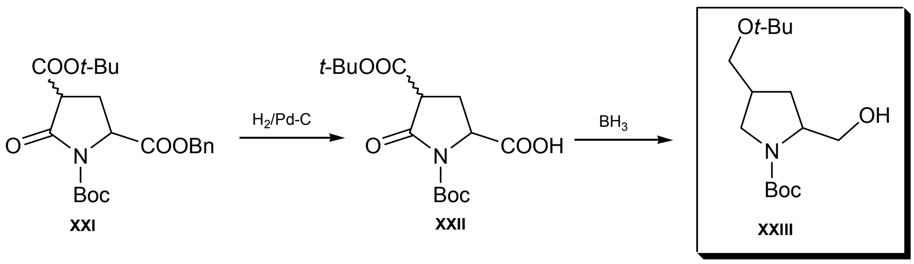
Indien de geïntroduceerde groep in de 4-plaats een voldoende goed elektrofiel was werd evenwel te cycliseren naar de 2-positie waargenomen (**XIX**).



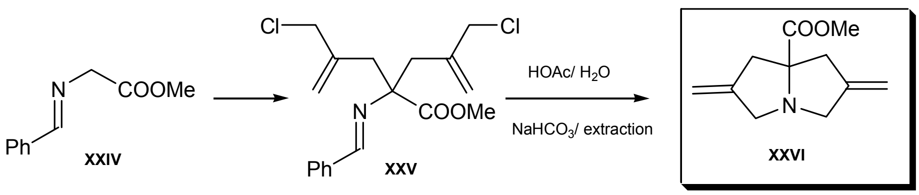
Een andere mogelijkheid om het 2-azabicyclo[2.1.1]hexaan skelet te bereiden werd geëvalueerd startend van het pyroglutamaat **XXI**. Het was de bedoeling de benzylester te ontschermen en het bekomen zuur selectief te reduceren tot het alcohol. Vervolgens zou dit alcohol kunnen omgezet worden tot een geschikte leaving groep waarna de ringsluiting naar de 4-positie zou kunnen geëvalueerd worden (**XX**). Het zuur **XII** werd gereduceerd met behulp van boraan maar dit leidde tot het t-butyl ether **XXIII**. Deze reactie was onverwacht omdat boraan de t-butylester reduceerde en zelfs naar de overeenkomstige ether **XXIII**.



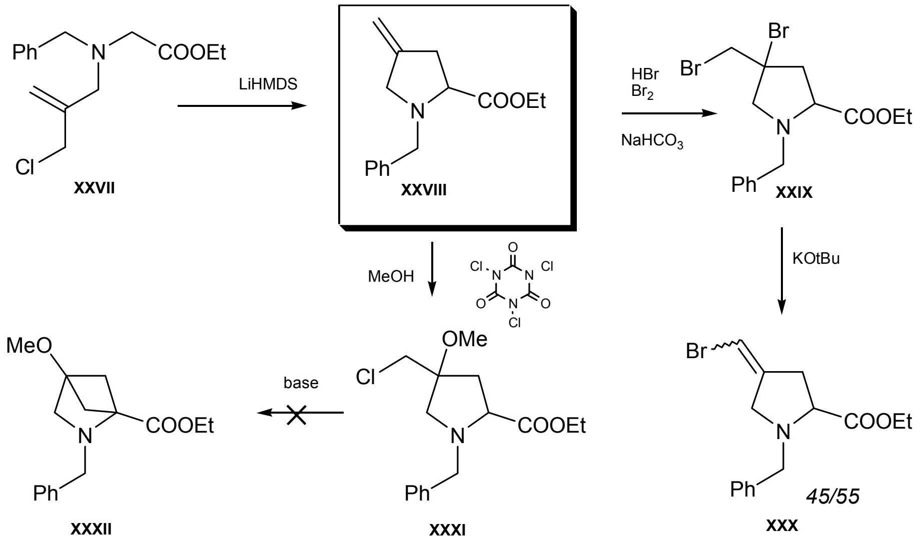
XX



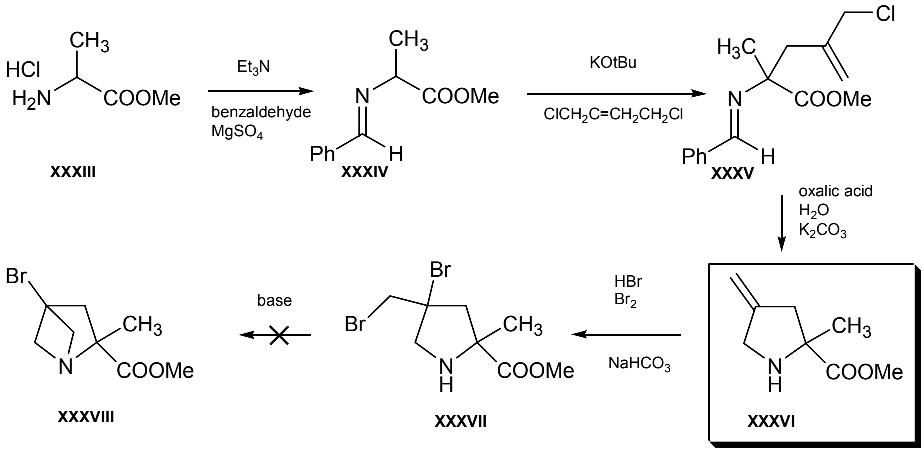
Verschillende toetredingen naar alkyl 4-methyleen-2-pyrrolidinecarboxylaten werden geëvalueerd. Pogingen om het imine **XXIV** éénmaal te alkyleren met 3-chloor-2-(chloormethyl)-1-propeen bleven zonder succes. In alle geëvalueerde omstandigheden werd het digealkyleerde imine **XXV** gevormd. Na hydrolyse en basische opwerking gaf dit aanleiding tot de vorming van het pyrrolizine **XXVI**.



Om deze dubbele alkylering te vermijden werd ethyl N-benzyl glycinaat gealkyleerd met 3-chloor-2-(chloormethyl)-1-propeen. Dit leidde tot **XXVII** en een geringe hoeveelheid dimeer wat verwijderd werd met behulp van flash chromatografie. Door een geschikte keuze van reactieomstandigheden kon deze verbinding **XXVII** omgezet worden tot het 4-methyleen-2-pyrrolidinecarboxylaat **XXVIII**. De additie van broom of methylhypochloriet aan de dubbele binding leidde tot de verbindingen **XXIX** en **XXXI** respectievelijk. Verschillende pogingen werden ondernomen om deze verbindingen te ringsluiten maar zonder gunstig resultaat.

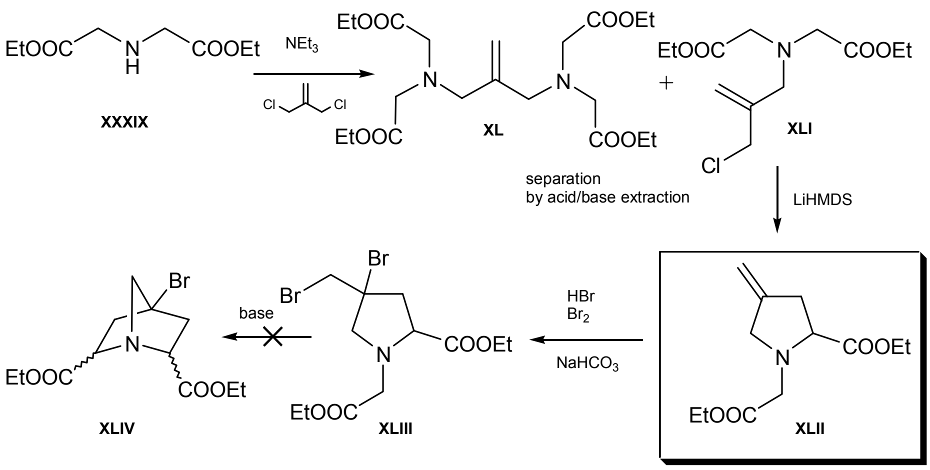


Een toetreding tot de synthese van het 1-azabicyclo[2.1.1]hexaan **XXXVIII** werd ondernomen vertrekkend van het imine **XXXIV**. Dit imine werd gealkyleerd met 3-chloor-2-(chloormethyl)-1-propeen en na hydrolyse werd het pyrrolidine **XXXVI** bekomen. Bromering van de dubbele binding leidde tot het pyrrolidine **XXXVII**. De mogelijkheid om deze verbinding te cycliseren tot **XXXVIII** werd geëvalueerd maar bleek eveneens onsuccesvol te zijn.



XXXIII XXXIV XXXV XXXVI XXXVII XXXVIII

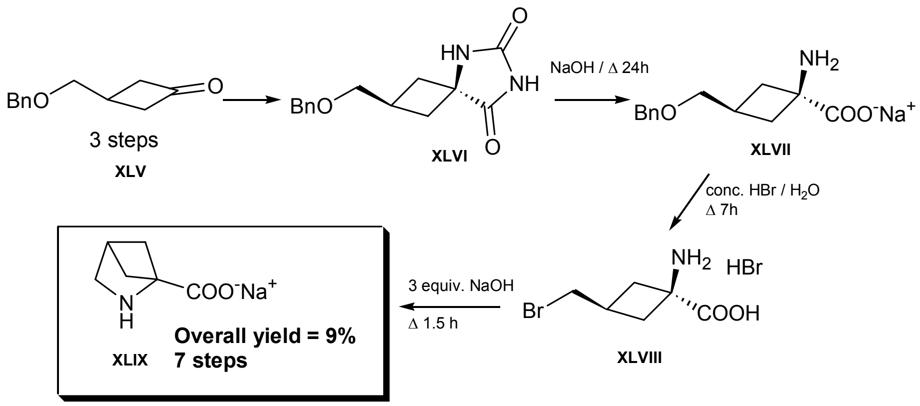
Het volgende schema geeft de toetreding tot het 1-azabicyclo[2.2.1]heptaan skelet weer uitgaande van **XXXIX**. Na reactie met 3-chloor-2-(chloormethyl)-1-propeen werd een mengsel van mono **XLI** en digealkyleerd product **XL** bekomen. Deze verbindingen konden eenvoudig gescheiden worden met behulp van een zuur/base extractie. Deprotonatie van **XLI** leidde tot het gewenste 4-methyleen-pyrrolidine **XLII**. Deprotonering van het gebromeerde product **XLIII** leverde niet het gewenste 1-azabicyclo[2.2.1]heptaan skelet.



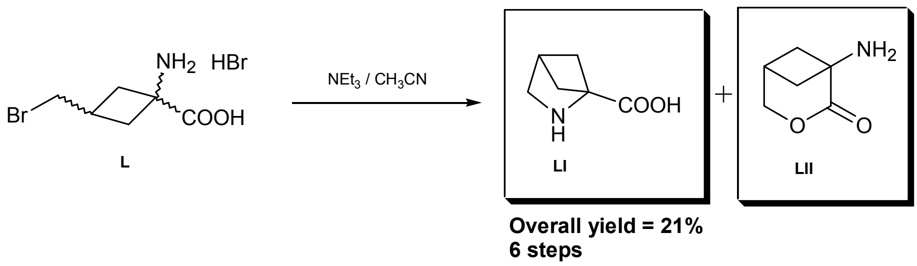
XXXIX XL XLI XLII XLIII XLIV

Omdat de vorming van een 4-ring in een bestaande 5-ring in geen enkel geval succesvol was, werden nieuwe strategieën ontwikkeld. In de volgende schema's wordt het 2-azabicyclo[2.1.1]hexaan skelet gevormd door ringsluiting van een geschikt cyclobutaan derivaat. Het natuurlijke 2,4-methanoproline kon gesynthetiseerd worden in 7 stappen uitgaande van allyl benzyl ether. Een [2+2]-cycloadditie reactie op dit alkeen leidde na verwijdering van de geminale chloor atomen tot het cyclobutanon **XLV**. De keto-functie werd omgezet tot een hydantoin (3/1 *cis/trans*) dat gehydrolyseerd werd tot het overeenkomstige aminozuur **XLVII**. Om 2,4-

methanoproline in zuivere vorm te bekomen, diende een scheiding van de isomeren te gebeuren ter hoogte van het hydantoin. Door middel van kristallisatie werd het *cis*-isomeer zuiver bekomen maar met laag rendement. De ether functie werd in één stap gehydrolyseerd en gederivatiseerd tot een broommethyl groep door het aminozuur **XLVII** te refluxen in een geconcentreerde HBr oplossing. Het bekomen aminozuur **XLVIII** kon in basisch milieu worden ringgesloten tot 2,4-methanoproline (Na-zout, 7 stappen, 9 % totaal rendement).

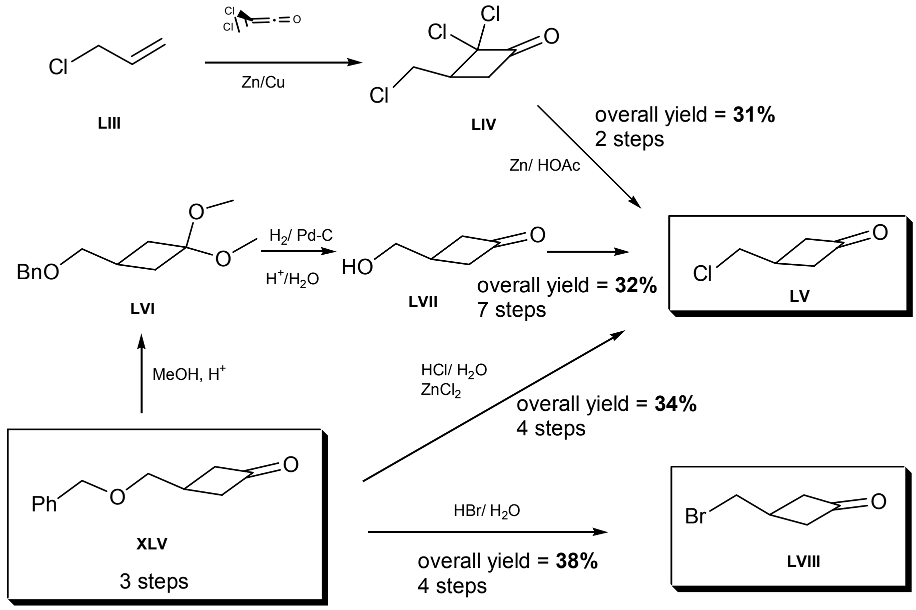


Omdat de scheiding van het hydantoin **XLVI** moeilijk bleek werd gezocht naar een alternatieve procedure. Een methode werd gevonden om de scheiding uit te voeren in de laatste stap. Door het aminozuur **L** (3/1 *cis/trans*) te verwarmen in acetonitrile werd enerzijds het natuurlijke 2,4-methanoproline en anderzijds het lacton **LII** bekomen. Deze verbindingen konden eenvoudig gescheiden worden door hun verschillende oplosbaarheid in organische solventen. Het rendement aan 2,4-methanoproline werd hierdoor aanzienlijk verhoogd (6 stappen , 21 % totaal rendement).



Omdat de cyclobutanon-chemie gunstige resultaten gaf werden reactieschema's opgesteld vertrekkend van het 3-chloormethylcyclobutanon **LV**. Tot op heden werd maar één bereiding van deze molecule beschreven in de literatuur. Deze is zeer lang en heeft een laag totaalrendement. Daarom werden eerst nieuwe reactieschema's tot 3-halomethylcyclobutanonen uitgewerkt.

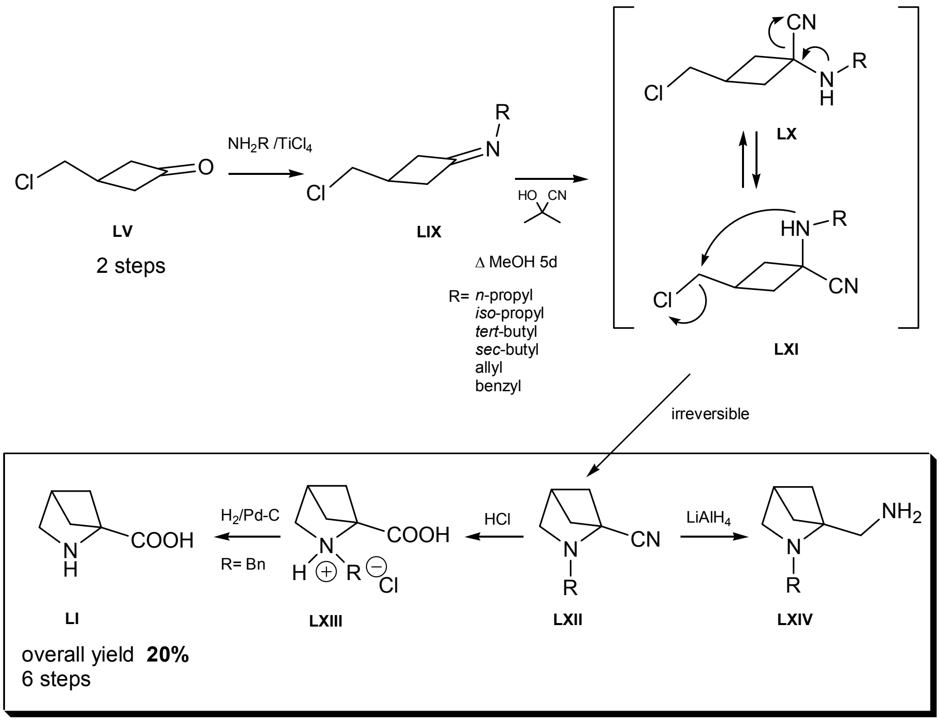
De kortste synthese was de cycloadditie reactie tussen allyl chloride en dichloorketeen. Het 3-chloormethylcyclobutanon **LV** werd bekomen na radicalaire dehalogenering van de twee geminale halogeen atomen (2 stappen, 31 % totaal rendement).



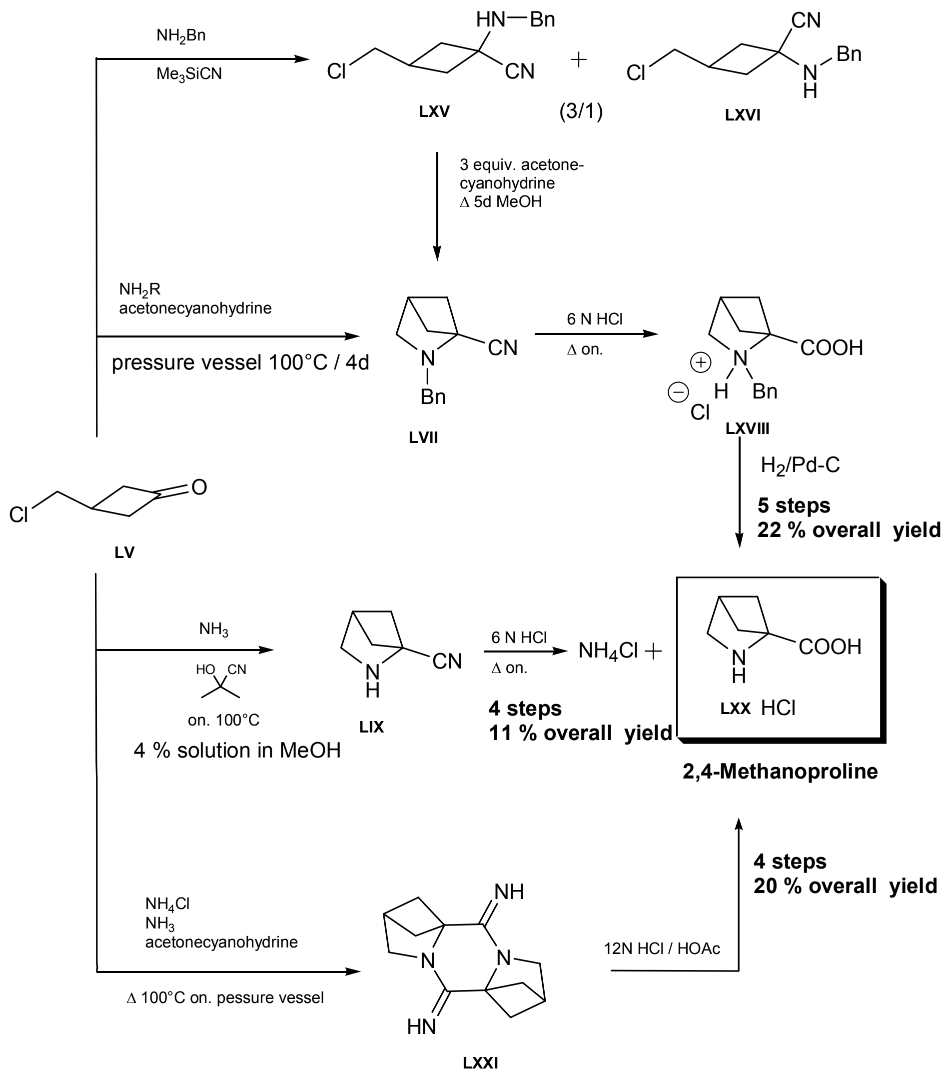
In een tweede sequentie werd vertrokken van het cyclobutanon **XLV**. Dit kon bereid worden op grote schaal en werd omgezet tot het 3-chloormethylcyclobutanon **LV** in 7 synthetische stappen (32 % totaal rendement).

Deze synthesesequentie kon ingekort worden door de ontscherming van de ether **XLV** en de omzetting van het bekomen alcohol tot een goede *leaving* groep in dezelfde stap uit te voeren (4 stappen, 34 % totaal rendement). Het 3-broommethylcyclobutanon **LVIII** kon eveneens bereid worden door gebruik te maken van geconcentreerd HBr in plaats van zoutzuur (4 stappen, 38 % totaal rendement).

Het 3-chloormethylcyclobutanon **LV** kon eenvoudig omgezet worden tot het overeenkomstige imine **LIX**. Dergelijke imines bleken evenwel zeer onstabiel te zijn in basische omstandigheden. Na een lange zoektocht werden reactiecondities gevonden die zowel de isomerisatie tussen de amino nitriles **LX** en **LXI** evenals de ringsluiting van **LXI** toelaten. Via dit protocol werden de imines **LIX** in één stap (zonder de vorming van neven producten) omgezet tot de bicyclische amino-nitriles **LXII**. Enerzijds leidde hydrolyse van de cyaangroep tot de aminozuren **LXIII** en anderzijds gaf reductie van deze functie aanleiding tot vorming van de overeenkomstige methylamines **LXIV**. Het natuurlijke 2,4-methanoproline kon verkregen worden door de N-benzyl groep van **LXIII** (R= Bn) te verwijderen (6 stappen, 20 % totaal rendement).

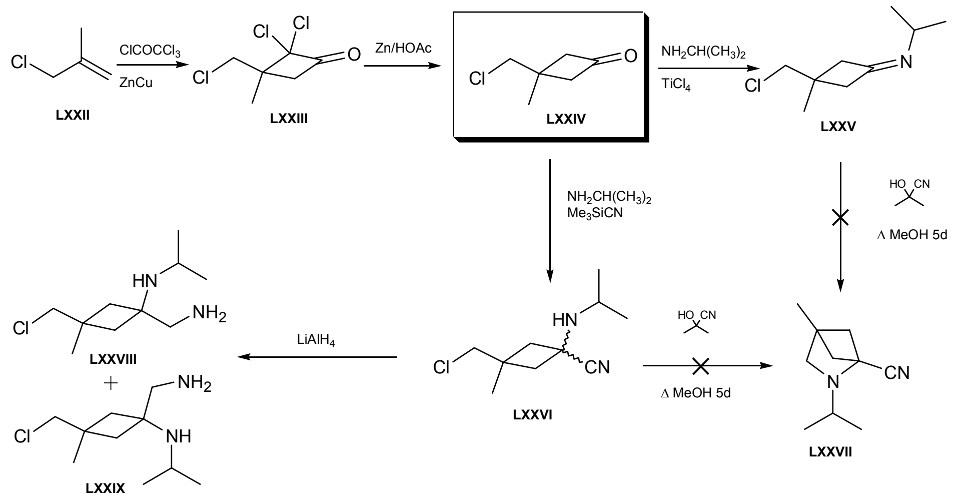


Het volgende schema geeft een overzicht van een aantal mogelijke synthese sequenties naar 2,4-methanoproline. Verschillende ‘shortcuts’ zijn weergegeven.

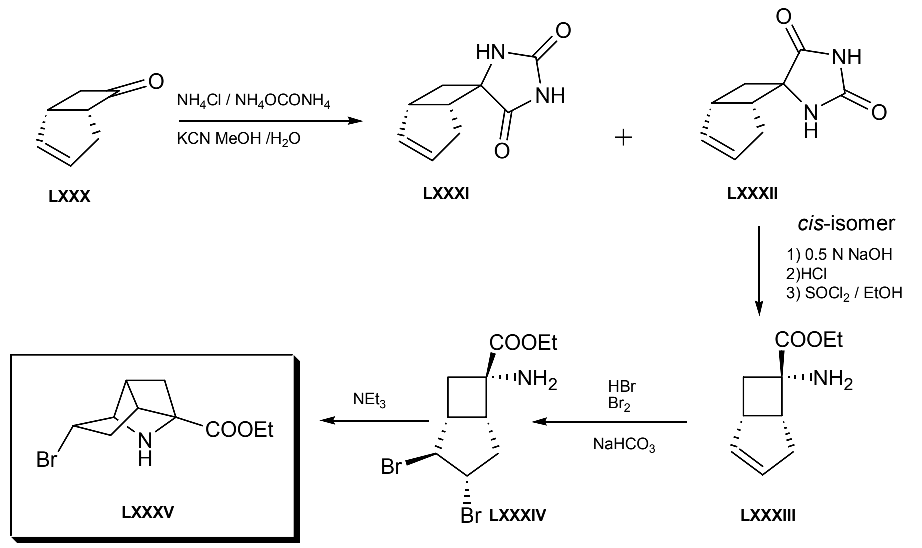


Zo werd onder andere door de N-bron te wijzigen de synthese sequentie ingekort tot 4 of 5 stappen waardoor 2,4-methanoproline kon bereid worden met een totaal rendement van 20 %.

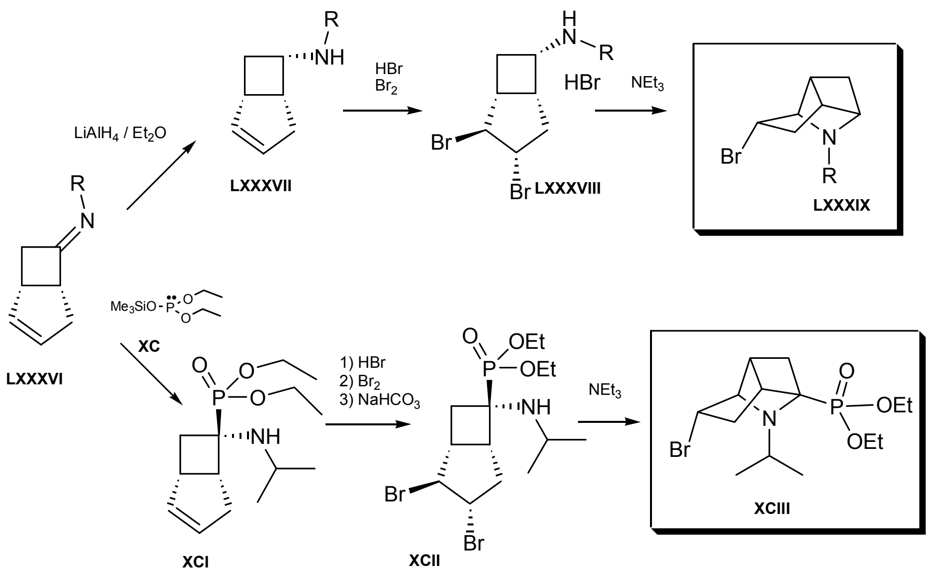
De mogelijkheid om 2-azabicyclo[2.1.1]hexanen te bereiden met een substituent op de twee bruggenhoofd koolstofatomen werd eveneens onderzocht. Daarvoor werd het cyclobutanon **LXXIV** bereid uitgaande van methallyl chloride **LXXII**. De ringsluiting van het imine **LXXV** werd geëvalueerd, maar de bicyclische verbinding **LXXVII** werd niet gevormd. Om de reactie verder te onderzoeken werden eerst de aminonitriles **LXXVI** bereid. Deze werden vervolgens gereduceerd tot **LXXVIII** en **LXXIX** maar ook hier werd geen ringsluiting waargenomen.



Het bicyclische keton **LXXX** werd gebruikt als uitgangsproduct voor de synthese van het 2-azatricyclo[3.3.0.0^{3,6}]octaan skelet. De keto-functie werd omgezet tot het overeenkomstige hydantoin (3/1 *cis/trans*). Hydrolyse en verestering leverden het amino ester **LXXXIII**. Na behandeling van het gebromeerde product **LXXXIV** met base werd het tricyclische skelet bekomen. Dit gespannen tricyclische amino ester **LXXXV** heeft het 2-azatricyclo[3.3.0.0^{3,6}]octaan skelet als basisstructuur.



Via een analoge sequentie konden tricyclische amines **LXXXIX** bereid worden. De imines **LXXXVI** werden gereduceerd met LiAlH$_4$ en de gevormde amines **LXXXVII** en **LXXXVIII** konden gescheiden door middel van kolomchromatografie. Na bromering en ringsluiting werden de tricyclische amines **LXXXIX** bekomen.



Deze methode was eveneens uitermate geschikt om tricyclische amino fosfonaten te bereiden. De diastereoisomere amino fosfonaten, verkregen na additie van fosfiet **XC** aan het imine **LXXXVI**, werden gescheiden en via een analoge sequentie omgezet tot het tricyclische amino fosfonaat **XCIII**.

Samengevat, werden in dit werk verschillende toetredingen tot het 2-azabicyclo[2.1.1]hexaan skelet geëvalueerd. Alle synthesewegen waar het bicyclische skelet diende gevormd te worden door synthese van een 4-ring in een bestaande 5-ring mislukten. Anderzijds waren de syntheses van 2,4-methanoproline en analoga vertrekkend van een geschikt cyclobutanon zeer succesvol.
Nieuwe bereidingen voor 3-halomethyl cyclobutanonen, welke de ideale uitgangsproducten voor de synthese van the 2-azabicyclo[2.1.1]hexaan skelet zijn, werden uitgewerkt.
Deze methodiek werd verder uitgebreid voor de synthese van tricyclische verbindingen. Een interessante toetreding tot het 2-azatricyclo[3.3.0.0^{3,6}]octaan skelet werd op punt gesteld. Op deze manier werden tricyclische amines, amino fosfonaten en een amino ester bereid.
Het gesynthetiseerde 2,4-methanoproline en analoga werden onderzocht op hun potentiele anti-feedant activiteit. Het natuurlijke 2,4-methanoproline vertoonde geen activiteit op de geteste larven, in tegenstelling tot een aantal derivaten die wel een anti-feedant activiteit vertoonden.
Enkele aspecten dienen verder onderzocht te worden zoals de omzetting van 3-chloormethyl cyclobutanon in één stap tot de 2-azabicyclo[2.1.1]hexane-1-carbonitriles en de asymmetrische bereiding van het 2-azatricyclo[3.3.0.0^{3,6}]octaan skelet wat mogelijks toepassingen kan hebben binnen de asymmetrische synthese.

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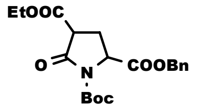
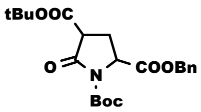
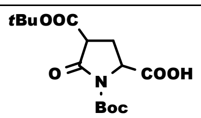
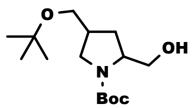
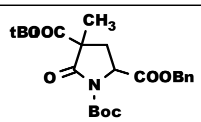
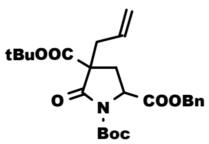
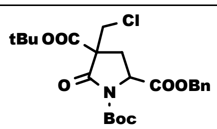
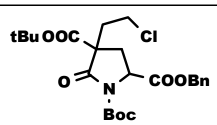
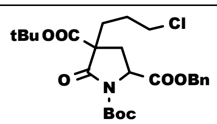
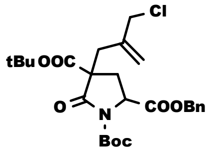
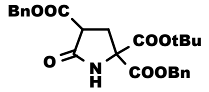
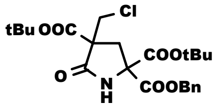
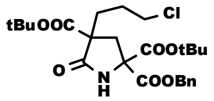
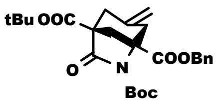
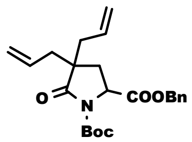
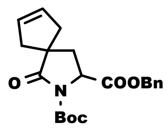
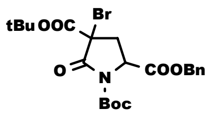
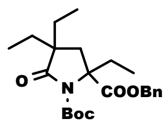
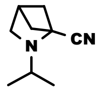
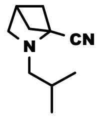
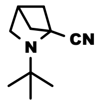
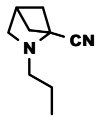
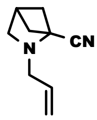
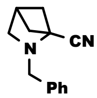
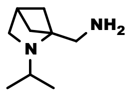
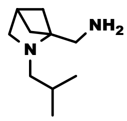
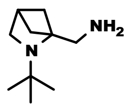
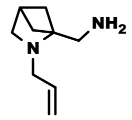
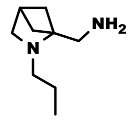
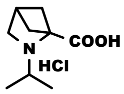
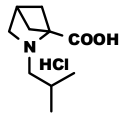
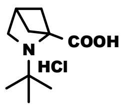
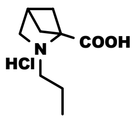
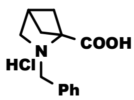
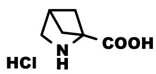
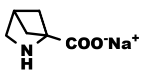
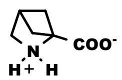
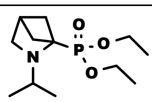
11. ^{13}C-values of the pyroglutamate derivatives

	C2	C3	C4
	57.25 57.68	25.34 24.73	48.50 48.82
	57.18 57.56	24.71 25.23	49.29 49.67
	57.16	25.34	49.43
	59.41	31.34	37.72
	56.87 56.12	33.78 33.41	53.37 53.10
	56.75 56.99	29.40 29.90	56.26 56.82
	56.39 56.78	28.77 29.29	59.19 59.55
	57.05 56.33	31.16 31.37	56.73 56.50
	56.85 56.24	31.18 30.98	56.99 56.73

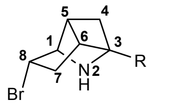
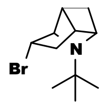
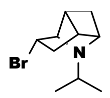
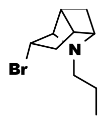
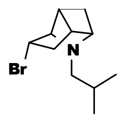
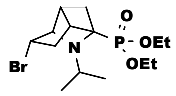
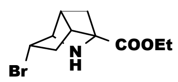
	56.91 57.22	31.61 30.39	57.22 57.45
	66.88 67.21	31.21 31.32	47.12 47.19
	66.31	34.44	57.68
	66.39	36.39	55.20
	64.71	37.48	56.24
	56.21	29.33	48.75
	56.48	38.01	50.49
	56.51 56.21	36.89 37.34	56.91 56.68
	65.64	36.42	47.62

12. ^{13}C-values of the 2-azabicyclo[2.1.1]hexanes

	C1 ($C_{quat.}$)	NCH_2	CH ring	CH_2 ring
	57.01	51.39	37.77	43.34
	59.84	56.12	38.99	42.25
	55.08	49.56	36.93	44.96
	59.50	55.18	38.94	42.05
	59.19	54.70	38.98	42.07
	59.42	54.82	38.99	42.05
	74.32	47.67	34.59	39.32
	74.18	58.35	36.42	37.72
	76.19	53.08	33.85	39.32

	74.61	57.23	36.26	37.41
	74.48	53.31	36.24	37.41
	75.99	57.14	35.61	36.28 45.42
	77.56	60.04	36.97	36.97 43.49
	75.36	55.32	33.98	37.43 45.17
	76.48	58.75	36.70	36.70 43.51
	77.68	56.74	37.07	37.16 44.06
	72.07	50.56	38.00	41.42
	71.42	48.31	37.33	42.22
	75.2	50.4	38.0	41.3
	67.81 d *J*= 174.6 Hz	47.30 d *J*= 13.4 Hz	37.56 d *J*= 26.9 Hz	41.71

13. ^{13}C-values of the 2-azatricyclo[3.3.0.0^{3,6}]octanes

	C1	C3	C4	C5	C6	C7	C8
	63.61	64.08	34.54	44.92	52.58	32.90	54.91
	67.89	63.79	29.99	45.10	51.36	32.87	54.02
	69.20	66.79	30.78	45.55	52.24	33.24	54.02
	70.60	66.61	31.11	45.52	52.24	33.39	54.81
	65.32 d *J*= 14.7 Hz	71.36 d *J*= 175.8 Hz	35.69 d *J*= 7.3 Hz	44.68 d *J*= 25.6 Hz	55.94	32.60	53.85
	63.18	70.26	39.01	43.47	54.00	32.97	55.38

14. Curriculum vitae

Personalia

Voornamen, naam	Thomas Joachim Landewald Rammeloo
Geboortedatum	27/12/1976
Geboorteplaats	Gent
Adres	Flamingostraat 7, 9000 Gent
E-mail	thomas.rammeloo@UGent.be trammeloo@yahoo.com
Telefoonnummer	09/242 04 47
Nationaliteit	Belg
Burgelijke staat	Gehuwd

Opleiding

1999 – 2003	Doctoraatsopleiding Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen
1994 – 1999	Bio-ingenieur in de scheikunde Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen, Universiteit Gent. Scriptie: Toetreding tot 2-azabicyclo[2.1.1]hexanen, het basisskelet van het anti-feedant 2,4-methanoproline, onder begeleiding van Prof. dr. ir. C. Stevens
1990 – 1994	Wiskunde – Wetenschappen, Koninklijk Atheneum Vilvoorde
1988 – 1990	Latijn-Wetenschappen, Middenschool Vilvoorde

Loopbaanoverzicht

Oktober 1999 – Oktober 2003	Doctoraatsonderzoek (IWT-bursaal): “Nieuwe toetredingswegen tot azabicycloalkanen met toepassingen binnen de agrochemie”, aan de Vakgroep Organische Chemie, Universiteit Gent (Promotor Prof. dr. ir. C. Stevens)

Congressen en studiedagen

- Met voordracht
  - VJC, 6de Vlaams Jongerencongres van de Chemie, (UIA) Antwerpen, België, 9-04-2002, Nieuwe toetredingswegen tot 2,4-methanoproline en analoga.
- Met poster
  - 6th Sigma-Aldrich Organic Synthesis meeting, Spa, Belgium 5-12-2002 tot 6-12-2002, Synthesis of α-aminophosphonates via iminium salts and subsequent ring closure to 4-phosphono-β-lactams
  - HRSMC (Holland Research School of Molecular Chemistry), Synthesis towards bioactive compounds, Arnhem, The Netherlands, 15-10-2001 tot 19-10-2001, Synthesis of 2,4-methanoproline and analogues based on the 2-azabicyclo[2.1.1]hexane skeleton
  - 4th Sigma-Aldrich organic synthesis meeting, Spa, Belgium 7-12-2000 tot 8-12-2000, Synthesis of 1-cyano-2azabicyclo[2.1.1]hexanes as precursors to 2,4-methanoproline
  - Belgium Organic Synthesis Symposium, Ghent, Belgium 10-07-2000 tot 14-07-2000, Synthesis of 2-alkyl 1-Boc pyroglutamtes via highly stabilised 4-litium enolates
  - Fifth IUPAC International Symposium on Bio-Organic Chemistry ISBOC-5, Pune, India, 30-01-2000, Synthesis of 2-azabicyclo[2.1.1]hexanes as analogues of the anti-feedant 2,4-methanoproline

Wetenschappelijke publicities met peer-review

- T. Rammeloo, C. V. Stevens, Synthesis of the new 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton as a constrained proline analogue, New Journal of Chemistry, 27, 668-671 (2003)
- C. V. Stevens, W. Vekemans, K. Moonen, T. Rammeloo. Synthesis of 4-phosphono-β-lactams via phosphite addition to acyliminium salts, Tetrahedron Letters, 44, 1619-1622 (2003)
- T. Rammeloo, C. V. Stevens, N. De Kimpe, Synthesis of 2,4-methanoproline analogues via an addition-intramolecular substitution sequence, J. Org. Chem., 67, 6509-6513 (2002)
- T. Rammeloo, C. V. Stevens, A new and short method for the synthesis of 2,4-methanoproline, Chem. Commun., 250-251 (2002)
- C. V. Stevens, T. Rammeloo, N. De Kimpe, Directing the regioselectivity of the alkylation of pyroglutamate carbamates by formation of a stable counter-ion complex, Synlett, 10, 1519-1522 (2001)
- C.V. Stevens, G. Smagghe, T. Rammeloo, 2,4-methanoproline derivatives: a quest for antifeedant activity, *J. Agric. Food. Chem.*, (artikel in voorbereiding)

Wetenschappelijke onderscheiding

- VJC-Exxon Mobil Prijs 2002: Laureaat voor beste voordracht binnen de sessie organische en polymeerchemie . Titel voordracht: Nieuwe toetredingswegen tot 2,4-methanoproline en analoga. (6de Vlaams Jongerencongres van de Chemie, (UIA) Antwerpen, België, 9-04-2002)

A man ceases to be a beginner in any given science and becomes a master in that science when he has learned that he is going to be a beginner all his life.

Robin G. Collingwood 1889-1943, British Historian, Philosopher